TO INVESTIGATE THE EFFECT OF FISH OIL CONTAINING PARENTERAL LIPID EMULSION ON INFLAMMATORY MARKERS, GAS EXCHANGE AND CLINICAL OUTCOMES IN SEPTIC PATIENTS.

by
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DECLARATION

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third-party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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ABSTRACT

Introduction

The effects of intravenous lipid emulsions containing fish oil in critically ill patients have not been studied widely and show conflicting results. This study compared the effects of a 4-oil lipid emulsion (SMOFlipid®) with a 100% soybean-based lipid emulsion in terms of biochemical parameters, inflammatory mediators, plasma total phospholipid fatty acid (FA) composition, sequential organ failure assessment (SOFA) score, gas exchange and clinical outcomes in patients with the systemic inflammatory response syndrome (SIRS) with or without sepsis.

Design

Double blind, randomised, single-centre study.

Method

Seventy-five patients predicted to need parenteral nutrition (PN) for ≥ five days were randomised to receive either a 4-oil lipid emulsion (Study Group (SG)) or a 100% soybean lipid emulsion (Control Group (CG)). Isocaloric, isonitrogenous PN was administered continuously. Routine biochemical measurements and gas exchange were assessed. SOFA score was calculated and plasma cytokines and total phospholipid FA composition was analysed.

Results

Both groups were well matched for baseline characteristics, but the SG had a trend to a higher mean APACHE II score (13.7 ± 7.5 versus 11.2 ± 8.1, p=0.19).

The nutritional intakes did not differ, except the SG received fish oil (FO), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and increased amounts of α-tocopherol and reduced amounts of phytosterols.

Triglycerides and Gamma-glutamyl transferase (GGT) levels increased in both groups. Bilirubin levels decreased in both groups between day 1 and 3 and then continued to decrease in the SG, but increased significantly in the CG after day 3. Concentrations of TNF-α decreased from day 1 to day 6 in the SG, whereas they increased in the CG, but the difference was not significant. Concentrations of interleukin-1β (IL-1β) and IL-6 decreased in the SG during the intervention and increased in the CG after day 3; however the difference was not significant at day 6. IL-10 concentrations decreased in both groups between day 1 and day 3, but increased from day 3 to day 6 in the SG. This difference was not significant (p=0.972).

Multiple positive changes in plasma total phospholipid FA percentages were demonstrated. Plasma EPA showed a significant increase in the SG (p<0.001). The n-6 polyunsaturated fatty acid (PUFA):n-3 PUFA ratio decreased in the SG and remained fairly constant in the CG.

A significant correlation was found for day 3 EPA intake and improvement in SOFA score. Days on mechanical ventilation and ICU LOS were not different between the two groups.

Conclusion

The results of this study suggest that PN containing a 4-oil LE with FO at a dose of 0.09 – 0.22g/kg in patients with SIRS, with or without sepsis, was associated with multiple changes in the plasma total phospholipid FA composition and a tendency to reduce plasma TNF-α and liver enzymes. There was no significant difference in terms of SOFA score, length of ICU stay and mortality. Additional studies need to be done in this patient population paying particular attention to the dose, duration and timing of FO and EPA per day and their effect on clinical outcomes.

OPSOMMING

Inleiding

Die uitwerking van intraveneuse lipiedemulsies (LE) wat visolie bevat is nie uitgebreid by krities siek pasiënte bestudeer nie en toon teenstrydige resultate. Hierdie studie het die uitwerking van 'n 4-olie lipiedemulsie (SMOFlipid®) met 'n 100 % sojaboon-gebaseerde lipiedemulsie vergelyk m.b.t. biochemiese parameters, inflammatoriese mediators, samestelling van totale fosfolipied- vetsuur (VS) in plasma, evaluering van opeenvolgende orgaanversaking (OOV)-telling, gaswisseling en kliniese uitkomste by pasiënte met sistemiese inflammatoriese responssindroom (SIRS), met of sonder sepsis.

Ontwerp

Dubbelblinde, ewekansige, enkel sentrum studie

Metode

Vyf-en-sewentig pasiënte by wie daar die behoefte voorspel was vir parenterale voeding (PV) van vyf dae, is ewekansig toegewys om óf 'n 4-olie lipiedemulsie (studiegroep (SG)), of 'n 100 % sojaboon-lipiedemulsie (kontrolegroep (KG) te ontvang. Isokaloriese, isonitrogene PV is deurlopend toegedien. Roetine biochemiese metings en gaswisseling is ondersoek. OOV -telling is bereken en plasma sitokiene en totale fosfolipied VS samestelling is ontleed.

Resultate

Beide groepe het goed ooreengekom betreffende hul basislyn eienskappe, maar die SG het 'n neiging gehad tot 'n hoër gemiddelde APACHE II - telling (13.7 ± 7.5 teenoor 11.2 ± 8.1, p = 0.19).

Die voedingsinnames het nie verskil nie, behalwe dat die SG visolie (VO), eikosapentaenoësuur (EPA) en dokosaheksaenoësuur (DHA), meer α-tokoferol en minder fitosterole ontvang het.

Trigliseriede en gamma-glutamieltransferase (GGT) vlakke het by beide groepe toegeneem. Bilirubienvlakke het by albei groepe tussen Dag 1 en 3 verlaag en toe aangehou om te daal by die SG, maar het beduidend gestyg by die KG na Dag 3. Konsentrasies van TNF-α het van Dag 1 tot Dag 6 in die SG gedaal, terwyl dit in die KG toegeneem het, maar die verskil was nie beduidend nie. Konsentrasies van interleukien-1β (IL-1β) en IL-6 het met die ingryping by die SG gedaal en na Dag 3 by die KG toegeneem, maar die verskil was nie beduidend op Dag 6 nie. IL-10 konsentrasies het by beide groepe tussen Dag 1 en Dag 3 afgeneem, maar toegeneem vanaf Dag 3 tot Dag 6 in die SG. Hierdie verskil was nie beduidend nie (p=0.972).

Veelvuldige positiewe veranderinge in die plasma se totale fosfolipied VS persentasies is aangetoon. Plasma EPA het 'n beduidende toename in die SG getoon (P<0.001). Die n-6 poli-onversadigde VS (POVS): n-3 POVS -verhouding het by die SG afgeneem en het redelik konstant by die KG gebly.

'n Beduidende korrelasie was aangetoon vir Dag 3 EPA inname en verbetering in OOV-telling. Dae op meganiese ventilasie en intensiewesorg eenheid (ISE) LVV het nie verskil tussen die twee groepe nie.

Gevolgtrekking

Die resultate van hierdie studie dui daarop dat PV wat 'n 4-olie LE met VO teen 'n dosis van 0,09 - 0,22 g/kg by pasiënte met SIRS met of sonder sepsis bevat, verband hou met veelvuldige veranderinge in plasma totale fosfolipied vetsuur samestelling en ’n neiging tot ’n verlaging in plasma TNF-α and lewerensieme. Daar was geen beduidende verskil in terme van die OOV –telling, lengte van ISE verblyf asook mortaliteit nie. Bykomende studies moet by hierdie pasiëntpopulasie gedoen word, met spesiale aandag aan die dosis, duur en tydsberekening van VO en EPA per dag en die uitwerking daarvan op kliniese uitkomste.

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CONTRIBUTIONS BY PRINCIPAL RESEARCHER & CO-RESEARCHERS

The principal researcher was responsible for protocol compilation, study planning and execution, data collection (with the help of the above-mentioned dietitians), data entry, and data analysis (with the help of a statistician) and writing of the thesis. The co-researchers provided guidance regarding the research process.

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LIST OF ABBREVIATIONS

AA	Arachidonic Acid
AAA:	Abdominal Aortic Aneurysm
ACCP	American College of Chest Physicians
ACS	Abdominal Compartment Syndrome
AEs	Adverse Effects
AGI	Acute Gastrointestinal Injury
AKIN	Acute Kidney Injury Network
ALA	Alpha Linolenic Acid
ANOVA	Analysis of Variance
APACHE II	Acute Physiology and Chronic Health Evaluation II
AKI	Acute Kidney Injury
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APP	Acute Phase Proteins
ARDS	Acute Respiratory Distress Syndrome
ASPEN	American Society of Parenteral and Enteral Nutrition
AST	Aspartate aminotransferase
BAPEN	British Association for Parenteral and Enteral Nutrition
BEE	Basal Energy Expenditure
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CCI	Chronic Critical Illness
CCCPG	Canadian Critical Care Practice Guidelines

CG	Control Group
CHO	Carbohydrate
CNS	Central Nervous System
CRP	C-Reactive Protein
CRRT	Continuous Renal Replacement Therapy
DAMPs	Damage-associated Molecular Patterns
DHA	Docosahexaenoic Acid
ECL	Endothelial Cell Lining
EE	Energy Expenditure
EFA	Essential Fatty Acid
EFAD	Essential Fatty Acid Deficiency
EN	Enteral Nutrition
EPA	Eicosapentaenoic Acid
EPaNIC	Early Parenteral Nutrition to supplement insufficient enteral nutrition in ICU patients trial
EPISEPSIS	EPIdemiology of SEPSIS
ESICM	European Society of Intensive Care Medicine
ESPEN	European Society of Clinical Nutrition and Metabolism
FA	Fatty Acid
FAMEs	Fatty Acid Methyl Esters
FBC	Full Blood Count
FFA	Free Fatty Acids
FFMI	Fat-Free Mass Index
FO	Fish Oil
GE	Gastric Emptying
GGT	Gamma-Glutamyl Transferase

GI	Gastrointestinal
GIT	Gastrointestinal Tract
GLA	Gamma Linoleic Acid
GRVs	Gastric Residual Volumes
IC	Indirect Calorimetry
IBW	Ideal Body Weight
ICU	Intensive Care Unit
IFALD	Intestinal Failure-Associated Liver Dysfunction
IL-1	Interleukin-1
IL-6	Interleukin-6
IL-10	Interleukin-10
INR	International Normalised Ratio
IV	Intravenous
IVLE	Intravenous Lipid Emulsion
KCs	Küpffer cells
KDIGO	Kidney Disease Improving Global Outcomes
LA	Linoleic Acid
LBM	Lean Body Mass
LCT	Long-Chain Triglyceride
LE	Lipid Emulsion
LFT	Liver Function Test
LOS	Length of Stay
LPL	Lipoprotein Lipase
LPS	Lipopolysaccaride
LTB_4	Leukotrienes B_4
LTB_5	Leukotrienes B_5

MAP	Mean Arterial Pressure
MCT	Medium-Chain Triglyceride
MODS	Multiple Organ Dysfunction Syndrome
MOF	Multi-Organ Failure
MUFA	Monounsaturated Fatty Acid
MV	Mechanical Ventilation
NO	Nitric Oxide
NPE	Non-Protein Energy
NRS	Nutritional Risk Screening
NT	Nutrition Therapy
NUTRIC Score	NUTrition Risk in the Critically Ill
ONS	Oral Nutritional Supplements
OO	Olive Oil
PAMPs	Pathogen-Associated Molecular Patterns
PCT	Procalcitonin
PGE_3	Prostaglandin E_3
PGE_5	Prostaglandin E_5
PICS	Persistent Inflammation, Immunosuppression, and Catabolism Syndrome
PN	Parenteral Nutrition
PNALD	Parenteral Nutrition-Associated Liver Disease
PROWESS	Protein C Worldwide Evaluation in Severe Sepsis
PRRs	Pattern recognition receptors
PUFA	Polyunsaturated Fatty Acid
QoL	Quality of Life
qSOFA	quick Sequential Organ Failure Assessment
RCT	Randomised Controlled Trial

RIFLE	Risk, Injury, Failure, Loss, End-Stage Renal Failure
ROS	Reactive Oxygen Species
SAE	Sepsis-Associated Encephalopathy
SBS	Short Bowel Syndrome
SCCM	Society of Critical Care Medicine
SECs	Sinusoidal Endothelial Cells
SFA	Saturated Fatty acid
SF-36	Medical Outcomes Study Questionnaire Short Form 36 Health Survey
SG	Study Group
SIRS	Systemic Inflammatory Response Syndrome
SO	Soybean Oil
SOFA	Sequential (Sepsis-related) Organ Failure Assessment
SNS	Sympathetic Nervous System
TE	Total Energy
TGs	Triglycerides
TICACOS	Tight Calorie Control Study
TNF	Tumour necrosis factor
TXA_3	Thromboxane A_3
TXA_2	Thromboxane A_2
VFD	Ventilator-Free Days
VLDL	Very Low Density Lipoproteins
VO_2	Oxygen Consumption
WCC	White Cell Count
WDGMC	Wits Donald Gordon Medical Centre

DEFINITION OF TERMS	
Acute Respiratory Distress Syndrome Berlin Definition	• Timing: Within 1 week of a known clinical insult of new or worsening respiratory syndrome • Chest imaging: Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules • Origin of oedema: Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic oedema if no risk factor present • Oxygenation: ○ Mild 200mmHg<PaO_2/FiO_2 ≤300mmHg with PEEP or CPAP ≥5cmH_2O ○ Moderate 100mmHg<PaO_2/FiO_2 ≤200mmHg with PEEP ≥5cmH_2O ○ Severe PaO_2/FiO_2 ≤100mmHg with PEEP ≥5cmH_2O (1)
APACHE II score	A scoring system for use in ICU patients to assess the severity of disease and provide an estimation of in-hospital mortality (2)
Nutrition Therapy	The provision of nutrients via an artificial route, i.e. enteral and/or parenteral nutrition (3). Nutrient provision is no longer regarded as supportive care in ICU, but rather as therapeutic intervention (4)
Parenteral Nutrition	Provision of nutrients intravenously (5)
RIFLE criteria	Classification scheme for acute renal failure which includes separate criteria for creatinine and urine output. RIFLE is Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage kidney disease (6).
Sepsis-3	Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in total (SOFA) score ≥ 2 points. Septic shock is defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone (7)
Sepsis	The systemic inflammatory response syndrome (SIRS) in the presence of infection (8)

Septic Shock	The presence of severe sepsis and haemodynamic instability despite adequate fluid resuscitation
Severe Sepsis	The presence of sepsis / SIRS with one or more organ dysfunction (8)
SIRS	A clinical syndrome that can be caused by a variety of insults, including infection, severe trauma, pancreatitis, burn injury and ischaemia. It is characterised by fever, tachycardia, tachypnoea, and an elevated white cell count as well as organ dysfunction and hypotension in severe cases (8)
SOFA	The Sequential/Sepsis-Related Organ Failure Assessment assesses the incidence and severity of organ dysfunction in critically ill patients (9)
qSOFA	Developed to rapidly identify adults with suspected infection following clinical criteria; respiratory rate of ≥22/min, altered mentation or systolic blood pressure of ≤100mmHg (7)

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CHAPTER 1

INTRODUCTION AND MOTIVATION

1.1 Significance of the study

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, characterised by a catabolic state and intense metabolic changes, resulting in malnutrition and impaired immune functions (1). 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 (2).

The inflammatory response to infection or injury is extremely complex. Even though it is a normal response following an insult, it can become uncontrolled, leading to additional tissue damage and multi-organ failure (MOF) (3). This response is initiated by activation of the innate immune system by pro-inflammatory stimuli such as DAMPs (damage-associated molecular patterns) and PAMPs (pathogen-associated molecular patterns) (4). The inflammatory process involves the release of pro- and anti-inflammatory cytokines. The pro-inflammatory cytokines released, includes the following cytokines 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 (2, 5). To balance and control inflammation, coexistent anti-inflammatory cytokines, IL-10 and IL-13, are produced in synchrony with pro-inflammatory ones (6).

Nutritional needs in the critically ill are poorly understood and vary with the phase of critical illness. Goals of nutrition therapy focus on attenuating the metabolic response to stress, preventing oxidative cellular injury, and favourably modulating the immune response (7). This includes providing adequate nutrition therapy, preventing any nutritional deficiencies, preserving lean body mass, maintaining glucose control, avoiding metabolic complications, decreasing infectious complications, and improving clinical outcomes (8).

Intravenous lipid emulsions (IVLE) in patients on parenteral nutrition (PN) not only are the main source of energy and fatty acids (FA) but remain associated with the development of adverse effects. Different types of lipid emulsions (LEs) have different effects on haematological 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. Pro-inflammatory properties of omega-6 polyunsaturated fatty acids (PUFAs) 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 polyunsaturated fatty acids (PUFAs), particularly fish oil, have beneficial effects on the immune system and organ function and improve clinical outcomes in surgical and acute respiratory distress syndrome (ARDS) patients. In addition, there is some promising data on their use in septic patients (9-11). The focus of this

research was to compare two different lipid emulsions (LEs) in critically patients requiring parenteral nutrition (PN).

To date there is no study looking at the use of a combination 4-oil lipid emulsion containing fish oil (SMOFlipid®) in septic patients. This lipid emulsion's efficacy and safety have been proved in paediatrics and in surgical patients; however there is limited data in septic patients. In South Africa, this LE is frequently used in intensive care units (ICUs) and it would thus be beneficial to have data showing improved oxygenation, reduced inflammation and improved outcome in this group of patients.

This thesis includes a comprehensive literature review, including a literature review which has been published in the *South African Journal of Clinical Nutrition*, a chapter discussing the methodology and an introduction to the results. The main result section is written as two manuscripts. The final chapter includes a discussion. Because this document is based on two manuscripts, the references are at the end of each chapter.

CHAPTER 2

LITERATURE REVIEW

This literature review focuses on the administration of different lipid emulsions, in particular omega-3 polyunsaturated fatty acids (PUFAs) 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 is addressed, focusing on how omega-3 PUFAs can attenuate inflammation to improve outcomes and reduce complications associated with the administration of parenteral nutrition.

2.1 Sepsis and the critically ill patient

Sepsis remains a common problem in critically ill patients. The incidence of sepsis is greater than 500 000 cases per year in the United States. The reported prevalence rates of the systemic inflammatory response syndrome (SIRS) in critically ill patients range from 20% to 60%., Approximately 40% of patients with sepsis may develop septic shock (12). Severe sepsis and septic shock have high mortality rates and are the leading cause of death in ICUs (13). Over the last decade, in-hospital mortality following severe sepsis has been reduced. Furthermore, mortality from acute lung injury has fallen dramatically (14). However, still more than 10 million people die annually of infection, according to the recent report by the Global Burden of Disease (15).

2.1.1 Definitions of sepsis

Infection induces sepsis, which is a syndrome of physiologic, biochemical and pathologic abnormalities (16). A consensus conference in 1991 (17) and 2001 (18) developed definitions for SIRS, sepsis, severe sepsis and septic shock (Table 2-1). These definitions have remained largely unchanged for more than two decades.

Table 2-1: Definition of sepsis (17, 18)

Diagnosis of SIRS – the presence of two or more of the following:

- Temperature >38 ^{o}C or <36 ^{o}C,
- Heart rate >90 bpm,
- Respiratory rate > 20 bpm or $PaCO_2$ <32 mmHg, and/or
- White blood count >12 000/mm^3, <4000/mm^3)

Sepsis: defined as suspected or proven infection plus SIRS.
Severe sepsis: defined as sepsis with organ dysfunction (hypotension, hypoxaemia, oliguria, metabolic acidosis and/or thrombocytopaenia).

Septic shock: defined as severe sepsis with hypotension despite adequate fluid resuscitation (17,18).

However, in 2014, the European Society of Intensive Care Medicine and the Society of Critical Care Medicine convened a task force to re-examine the above definition and proposed a new definition of sepsis, termed *Sepsis-3* (Table 2-2). The task force recommended the use of Sequential (Sepsis-related) Organ Failure Assessment (SOFA) scoring to define the organ dysfunction of a potentially septic patient. The SOFA score is discussed in more detail in scoring systems.

Table 2-2: *Sepsis-3* Terms and Definitions (16)

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Organ dysfunction can be identified as an acute change in total (SOFA) score ≥ 2 points.
- Septic shock is defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Clinically identified as:
    - Vasopressor requirement to maintain a mean arterial pressure (MAP) ≥65 mm Hg.
    - Serum lactate level > 2mmol/L in the absence of hypovolaemia.

Owing to the complexity of the SOFA score, the use of *Sepsis-3* in practice may prove to be impractical. Thus, the task force described an easier method, *quick* SOFA (qSOFA), to facilitate the identification of patients potentially at risk of dying of sepsis outside the ICU. The qSOFA only has 3 components that are each allocated 1 point. A qSOFA score ≥ 2 points to a high probability of death or deterioration requiring ICU (19). This is discussed in more detail under the scoring systems section.

The above definition was not used in this research project as the original protocol was written in 2012; however the SOFA score was calculated for each patient.

2.1.2 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 to survive the injury. Sir David Cuthbertson described several phases of the metabolic response over time, including the 'ebb' phase and the 'flow' phase. More recently, the chronic or post-injury phase has been added as a third sequence, frequently encountered in the Intensive Care Unit (ICU) (2). The ebb phase occurs several hours after the injury, and lasting for 12 to 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 (20). The post injury or anabolic phase lasts for some weeks, as protein and fat stores are restored and weight regained (5).

The metabolic response to stress involves a neuroendocrine and an inflammatory component. Hormones released from the adipose tissue and from the gastrointestinal tract (GIT) can also play an important role in this response. The sympathetic nervous system (SNS) is activated when a stressor is detected and is involved in the activation of adrenergic receptors resulting in the immediate release of norepinephrine and epinephrine into the bloodstream (2). The activation of the hypothalamus–pituitary axis results in the release of adrenocorticotropic hormone, thyroid-stimulating hormone, growth hormone, follicle-stimulating hormone, and luteinising hormone by the anterior pituitary gland. The circulating levels of hormones released from peripheral glands are decreased in response to this, with the exception of cortisol. Cortisol is a catabolic hormone that mobilises energy stores. It promotes gluconeogenesis in the liver, leading to raised blood glucose levels (2, 20).

During the chronic phase, the plasma levels of both pituitary factors and peripheral hormones are lowered; however, a peripheral resistance to the effects of growth hormone, insulin, thyroid hormone, and cortisol persists. These hormonal alterations affect the energy, protein and fat metabolism (2) resulting in negative nitrogen balance, weight loss and hyperglycaemia (5).

The inflammatory component is partially regulated by the central nervous system via cytokines and inflammatory mediators. Inflammation is triggered when innate immune cells detect tissue injury or infection. Surveillance mechanisms involve pattern recognition receptors (PRRs) in the cytoplasm and on the cell surface. These receptors detect, either directly or indirectly, pathogen-associated molecular patterns (PAMPs) or host-derived damage-associated molecular patterns (DAMPs) released by injured cells and respond by triggering activation of NF-κB and other transcription factors promoting pro-inflammatory and profibrotic pathways (4). The inflammatory process involves the release of pro- and anti-inflammatory cytokines. Anti-inflammatory cytokines

act to localise and prevent overexuberant inflammation; it is the loss of this local control that leads to SIRS, Multi-Organ Dysfunction Syndrome (MODS), shock, and death (6).

The pro-inflammatory cytokines released, includes the following cytokines, 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 reticulo-endothelial cells (lymphocytes, macrophages and monocytes), promote wound repair and induce the production of other cytokines (2,5). To balance and control inflammation, coexistent anti-inflammatory cytokines, IL-10 and IL-13, are produced in synchrony with pro-inflammatory ones (6). In addition to typical clinical signs of sepsis, like fever and lethargy, these cytokines also induce weight loss, proteolysis and lipolysis. They also trigger anorexia at the hypothalamic level (2).

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 (6). Levels of these cytokines were measured during the first 6 days in ICU in this research project.

Adipokines are also released from the different cell types of fat tissue and are being investigated as potential contributors to metabolic changes related to sepsis. The role played by hormones released by the gut is also under investigation, indicating that circulating levels of ghrelin are mostly decreased, while levels of cholecystokinin and peptide YY are increased. These changes have been related to anorexia, which is a common behavioural adaptation to stress (2).

Recently, the term 'persistent inflammation, immunosuppression, and catabolism syndrome' (PICS) has been used to describe the most recently 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) responses. In some cases, the SIRS becomes overwhelming, leading to early MOF and death. Fortunately, modern ICU care is directed at early recognition of shock and treatment. If patients do not die of early MOF, there are two possible pathways. Either their abnormal immunology rapidly recovers, 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 (3).

2.1.3 Role of autophagy in sepsis

Autophagy acts as a survival mechanism under conditions of stress, maintaining cellular integrity by regenerating metabolic precursors and clearing subcellular debris. This process contributes to basal cellular and tissue homeostasis. Autophagy participates in the turnover of mitochondria and other organelles and is involved in the clearance of polyubiquitinated protein aggregates which accumulate during stress and disease. Autophagy has also been implicated as a regulator of lipid metabolism. It acts primarily as a protective mechanism that may prevent cell death (21).

During infection, autophagy assists in the immune response by degrading intracellular bacteria and viruses. It contributes to the suppression of inflammation, including the down-regulation of both interferon and pro-inflammatory cytokines, through the preservation of mitochondrial function (21).

In an animal model, the administration of parenteral nutrition (PN), in particular protein and lipids rather than glucose, in the early phase of critical illness evoked a phenotype of autophagy deficiency in the liver and skeletal muscle (22) and is thought to increase muscle weakness and impair the recovery thereof (23). Current therapeutic targeting of autophagy is limited by an incomplete understanding of how the process contributes to pathogenesis, the lack of specificity of compounds that can influence autophagy, and the clinical efficacy. An improved understanding of the mechanism by which autophagy can prevent pathogenesis may lead to the identification of new targets for both diagnostic and therapeutic approaches (21).

2.1.4 Scoring systems

Various scoring systems have been developed in the ICU to predict patient outcome, comparing quality of care and stratification for clinical trials. Even though disease severity scores are not the key elements of treatment, they are, however, an essential part of improvement in clinical decisions and in identifying patients with unexpected outcomes. Accurate diagnostic criteria and consensus definitions have an important role in adult intensive care medicine, providing tools for research, benchmarking, performance monitoring and accreditation (24).

The APACHE II was developed in 1985 and is a severity of disease classification system. It uses a points system based upon values of 12 routine physiologic measurements (taking the worst measurements during the first 24 h after stabilisation), age and previous health status to provide a general measure of severity of disease. An integer score from 0 to 71 is then computed based on these measurements: higher scores imply a more severe disease and a higher risk of death (see Appendix A: APACHE II score) (24, 25).

The Sequential (or sepsis-related) Organ Failure Assessment (SOFA) assesses the incidence and severity of organ dysfunction in critically ill patients (Table 2-3). It is a simple, effective method to describe organ dysfunction and/or failure in critically ill patients. Regular, repeated scoring

enables patient disease development and condition to be monitored (26) (Table 2-4). Recently, the Third International Consensus Definitions for Sepsis and Septic Shock (*Sepsis-3*) was published. *Sepsis-3* emphasised the value of a change of 2 or more points in the SOFA score, which was associated with an in-hospital mortality rate greater than 10%. They also introduced quick SOFA (qSOFA), where adults out of hospital, in emergency departments or general hospital ward settings, with suspected infection, can be rapidly identified as being more likely to have poor outcomes typical of sepsis if they have at least 2 of the following clinical criteria: respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of ≤100mmHg (16).

Table 2-3: Sequential (sepsis-related) Organ Failure Assessment Score (26)

SOFA Score	**0**	**1**	**2**	**3**	**4**
				With respiratory support	
Respiration PaO_2/FiO_2 mmHg	> 400	≤ 400	≤ 300	≤ 200	≤ 100
Coagulation, platelets X $10^3/mm^3$	> 150	≤ 150	≤ 100	≤ 50	≤ 20
Liver, bilirubin mg/dl (µmol/l)	<12 (<20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (>204)
Cardiovascular, hypotension	No hypotension	MAP < 70mmHg	Dopamine ≤5 or Dobutamine (any dose)	Dopamine >5 or ephinephrine (adrenaline) ≤ 0.1 or norepinephrine ≤ 0.1 (noradrenaline)	Dopamine >15 or ephinephrine (adrenaline) > 0.1 or norepinephrine (noradrenaline) > 0.1
Central Nervous System GCS Score	15	13–14	10–12	6–9	<6
Renal, creatinine mg/dl (µmol/l) or urine output	<1.2 (<110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440) or <500ml/day	>5.0 (>440) or <200ml/day
Abbreviations: PaO_2/FiO_2: ratio of arterial oxygen partial pressure to fractional inspired oxygen, GCS: Glascow Coma Scale.					

Sepsis results from a dysregulated inflammatory response to infection and leads to organ dysfunction, which is associated with high morbidity and mortality. The use of severity scores in the ICU, such as the SOFA score mentioned in *Sepsis-3*, can help predict in-hospital mortality and qSOFA can rapidly identify patients likely to have poor outcomes (19).

2.1.5 Signs of sepsis

Diagnosing sepsis relies on assessing a variety of nonspecific signs, symptoms, examination findings and laboratory values. A list of signs and symptoms to be considered in clinical practice is tabulated below. Owing to the lack of specificity of some variables and the variable time course during which some clinical criteria appear, the diagnosis of sepsis is often more apparent in retrospect than during the prospective reality of clinical care. Absolute confirmation of the diagnosis is not expected in the early phase of the disease. Blood cultures remain an important part of the diagnostic strategy in sepsis (19).

Table 2-4: Clinical signs of sepsis (19, 27)

General signs and symptoms
Rigors, fever or hypothermia
Tachypnoea/respiratory alkalosis
Positive fluid balance, oedema
Generalised haematological/inflammatory reactions
Increased (sometimes decreased) white blood cell count
Increased inflammatory markers (C-reactive protein, procalcitonin, interleukin-6)
Haemodynamic alterations
Hypotension: low mean or systolic arterial pressure
Unexplained tachycardia
Increased cardiac output
Unexplained high cardiac output/low systemic vascular resistance/high SvO_2
Altered skin perfusion, decreased capillary refill or mottling
Decreased urine output
Unexplained hyperlactataemia/increased base deficit
Signs of organ dysfunction
Acute lung injury: arterial hypoxaemia
Altered mental status
Unexplained alterations in renal function
Hyperglycaemia or hypoglycaemia
Coagulopathy: Elevated prothrombin or partial thromboplastin time or low platelets
Unexplained alterations in liver enzymes (hyperbilirubinaemia, transaminitis)
and function (INR, ammonia)
Intolerance of feeding (altered gastrointestinal motility, ileus)

2.1.6 Consequences of sepsis

The inflammatory response to infection or injury is extremely complex. Even though it is a normal response following an insult, it can become uncontrolled, leading to additional tissue damage and multi-organ failure (MOF) (3).

Data from recent years reveal as much as 40–50% of mortality occurs after the patient leaves the ICU within 12 months of an admission and could occur up to two years after an event. The survivors of sepsis often have a reduced quality of life (QoL) owing to long-term physical, cognitive, and psychosocial morbidity. Many patients that are placed in nursing homes or rehabilitation centres may never return home or to a meaningful quality of life (14, 28, 29).

2.1.6.1 Pulmonary function

The lungs are frequently affected in patients with sepsis either directly as the focus of infection or as part of multiple organ dysfunction. Thus, bacterial pneumonia and acute respiratory distress syndrome (ARDS) are the conditions in sepsis that most commonly result in patients requiring respiratory support (28).

ARDS is marked by inflammation, increased permeability of alveolar membranes, and cytokine activation. Damage to the endothelium, or lining of the capillary, interferes with alveolar gas exchange. The damage causes macrophages to release cytokines, including TNF-α, IL-1β and IL-6, inflicting more damage on the alveolar endothelium. Protein levels build, pulling fluid into the alveolar spaces and causing non-cardiac pulmonary oedema and reduced surfactant level. Normally, surfactant decreases surface tension and allows the alveoli to open easily. In ARDS, the oedema and reduced surfactant level compromise gas exchange, causing decreased oxygen and increased carbon dioxide in the blood. The result is hypoxaemia, pulmonary hypertension, and decreased pulmonary compliance. The persistent production of oxygen-free radicals and arachidonic acid inflammatory mediators worsen lung inflammation, oedema and diffuse alveolar damage. In later stages of ARDS, progressive alveolitis and fibrosis further decrease pulmonary function (30, 31).

Supportive care should include:

- Prevention of pulmonary failure in sepsis.
- Closed-loop control of mechanical ventilation to maintain consistent pressure and flow waveforms in the face of changing patient conditions (32) and lung protective ventilation in patients with ARDS, maintaining low inspiratory driving pressure, with low tidal volumes, with limited airway pressure and high levels of positive end-expiratory pressure (33).
- Implementation of clinical pathways for rescue therapies for severe hypoxia (28).

ARDS patients have a severely compromised nutritional status and nutrition therapy should be started as soon as possible (31). Patients with ARDS often require PN with lipid emulsions (LEs) as essential components. Besides energy supply, these LEs might display differential modulatory effects on lung integrity and inflammation. LEs have an ability to alter cytokine release , to modify leukocyte function, and to influence the generation of lipid mediators that display both pro-and anti-inflammatory properties (31, 34). This is discussed in more detail in Section 2.3.4.2.2 of this review.

2.1.6.2 Liver function

Acute liver failure was defined by at least two of the following items: (a) bilirubin level of > 43 µmol/L (b) serum alanine aminotransferase (ALT) concentration of more than twice the upper limit, and (c) prothrombin time of > 1.5 times the control value or an international normalised ratio (INR) of > 1 (35). During sepsis, liver dysfunction is one of the multiple organ dysfunction syndrome (MODS) components and is usually associated with a poor prognosis. The incidence of liver dysfunction remains unclear. The liver plays a pivotal role in regulating a wide range of key metabolic, homeostatic, and host-defence activities. Shock and initial tissue hypoperfusion could contribute to liver dysfunction. The lack of reliable diagnostic tools militates against detection of early liver dysfunction (36).

The liver has a role in bacterial and endotoxin scavenging, detoxification, and synthesising proteins for metabolic, coagulation and immune functions. Liver perfusion, which represents 25% of cardiac output, is required to ensure the above functions. The portal venous blood flow regulated by the hepatic arterial buffer response, compensates for any reduction in portal blood flow. During the course of septic shock, the liver contributes actively to tissue repair and host defence through cross-talk between hepatic and blood cells. The hepatic cells will shift their metabolic pathway towards up-regulation of the inflammatory response, which is responsible for an increase in the synthesis of acute-phase proteins mediated predominantly by IL-6. This shift leads to increases in fibrinogen, prothrombin, C-reactive protein, α-1-antitrypsin, and haptoglobin levels, whereas the hepatic production of albumin, transferrin and antithrombin is decreased. The up-regulation of the acute-phase proteins inhibits the protein C pathway and results in profound changes in pro-coagulant activity in sepsis. Glucose metabolism is also significantly altered owing to increases in glycogenolysis and gluconeogenesis, and increased amino-acid uptake during liver hypermetabolism (36).

The Küpffer cells (KCs) are involved in scavenging bacteria and endotoxin. The liver harbours approximately 80% of all macrophages in the human body as resident KCs. In the case of underlying liver disease, endotoxin clearance is impaired resulting in a higher susceptibility of the host to infection. KCs can produce various pro-inflammatory mediators, including TNF-α, acute-phase proteins and nitric oxide (NO). KCs also interact with blood cell components (platelets, erythrocytes and leukocytes), promoting neutrophil recruitment in the sinusoids and enhancing

the pro-inflammatory response. Liver microvascular perfusion can become impaired through the adhesion of neutrophils to sinusoidal endothelial cells (SECs) , promoting thrombus formation in the sinusoids (36).

Several cytokines can induce hepatocellular dysfunction. TNF-α is considered to be the main cytokine of SIRS development and can directly stimulate hepatocytes to induce IL-6 production. IL-6 is considered the main cytokine implicated in the liver inflammatory response and is also produced by SECs, KCs and hepatocytes after liposaccharide (LPS) stimulation. In combination with IL-1 and TNF-α, IL-6 is widely involved in the stimulation of acute-phase protein (APP) production (36). Lipid mediators such as platelet-activating factor and arachidonic acid metabolites, metabolised from n-6 polyunsaturated fatty acids (PUFA), are pro-inflammatory and can promote direct liver injury (37).

The SOFA score uses bilirubin to determine liver dysfunction over the course of sepsis. Using the SOFA score, the French EPISEPSIS (EPIdemiology of SEPSIS) study group reported incidences of liver dysfunction (hepatic score of 3 or 4) of 46.6% and 6.3% respectively, in 541 patients with severe sepsis during the first 24 hours after admission to the ICU (38). In the same patient population, with the same score, the PROWESS (Protein C Worldwide Evaluation in Severe Sepsis) trial reported incidences of liver dysfunction (hepatic score of 1 or 2) and liver failure (hepatic score of 3 or 4) of 35.6% and 2.75% respectively (39). Both the EPISEPSIS study and PROWESS trial found that the persistence or development of liver failure after the onset of severe sepsis was strongly associated with poor outcome and a lower 28-day survival rate respectively (36).

2.1.6.3 Gut function

Gut failure or gastrointestinal (GI) dysfunction frequently occurs in seriously ill patients and is responsible for bacterial translocation. This could cause sepsis with the initiation of SIRS and MODS and/or death. Delayed gastric emptying, abnormal motility patterns, and impaired intestinal barrier integrity, are commonly observed in the ICU. It has been recognised that a functional gastrointestinal tract (GIT) is an important factor in clinical outcome of patients in the ICU (40).

Several factors related to critical illness have been reported to be associated with gastric dysmotility and feed intolerance, including hyperglycaemia, deranged electrolyte levels, the nature of the acute illness, mechanical ventilation, intra-abdominal hypertension, raised intracranial pressure, sedatives, cytokine release, and splanchnic hypoperfusion due to shock and sepsis (40, 41). Nguyen et al. assessed the impact of admission diagnosis on gastric emptying (GE) in critically ill patients and found the highest occurrence of delayed GE was observed in patients with head injuries, burns, mechanical ventilation (MV), multi-system trauma, and sepsis (41).

Intestinal function is an important determinant in the outcome of patients admitted to ICU and the development of GI problems is related to worse outcomes in critically ill patients. Until 2011

there was no clear definition of gastrointestinal function in ICU. The ESICM Working Group on Abdominal Problems suggested the following definition for acute gastrointestinal injury (AGI) (42).

Table 2-5:The four grades of severity of AGI (42)

AGI Grade I	Increased risk of developing GI dysfunction or failure. The function of the GI tract is partially impaired, e.g. postoperative nausea and/or vomiting, absence of bowel sounds.
AGI Grade II	GI dysfunction that requires intervention. The GI tract is unable to perform digestion and absorption adequately to satisfy the nutrient and fluid requirements of the body, e.g. gastroparesis with high gastric residual volumes (GRVs) or reflux, paralysis of the lower GI tract, and diarrhoea.
AGI Grade III	GI failure. Loss of GI function, where restoration of function is not achieved despite interventions and the general condition is not improving, e.g. feeding intolerance persists, despite treatment, high GRVs, persisting GI paralysis, increasing intra-abdominal pressure.
AGI Grade IV	Dramatically manifesting GI failure, a condition that is immediately life-threatening, e.g. bowel ischaemia with necrosis, GI bleeding leading to haemorrhagic shock, abdominal compartment syndrome requiring decompression.

Primary AGI is associated with direct injury to the organs of the GI system or a primary disease, e.g. peritonitis, pancreatic or hepatic pathology, abdominal trauma or surgery (42).

Secondary AGI develops as the consequence of a patient's response to critical illness without primary pathology in the GI system, e.g. GI malfunction in patients with pneumonia, non-abdominal surgery or trauma, post-resuscitation state and cardiac pathology (42).

Septic shock, with excess nitric oxide (NO) production, can cause a paralytic ileus that can lead to a delay in the institution of enteral feeding. Narcotics and muscle relaxants can further worsen GI tract motility, interfering with the optimal protein and energy intake in critically ill patients (12).

2.1.6.4 Renal function

Sepsis is the most frequent contributing factor to the development of acute kidney injury (AKI) in critically ill patients. The incidence of AKI in adult ICU settings has been reported by the consensus AKI definition criteria by Risk, Injury, Failure, Loss, End-Stage Kidney Disease (RIFLE), Acute Kidney Injury Network (AKIN) and, most recently Kidney Disease Improving Global Outcomes (KDIGO), to range between 16% and 67% and sepsis accounts for 26% to 50% of patients (43).

Septic AKI is associated with greater derangement in haemodynamic and laboratory parameters, greater severity of illness and higher need for MV and vasopressor therapy resulting in a higher in-hospital mortality compared with non-septic AKI. Populations that are at risk of developing sepsis-associated AKI are elderly, female patients with baseline comorbidities, specifically chronic renal failure, diabetes, heart failure, liver infection and malignancy (43). The causes of AKI are multifactorial. The mechanism is complex and most likely involves a decrease in effective intravascular volume resulting from systemic hypotension, release of pro-inflammatory cytokines, ischaemia-reperfusion injury to the glomerulus, hypoxic or oxidative stress, direct renal vasoconstriction and activation of neutrophils by endotoxins and other peptides, which contribute to kidney injury. Additional risk factors like nephrotoxic drugs and volume overload with venous congestion may further aggravate the situation (28, 43).

Renal support in sepsis includes early diagnosis, conservative measures and extracorporeal therapies. Currently, the major strategies for therapy include optimising renal perfusion by using vasopressors and volume resuscitation while avoiding volume overload and interstitial oedema (28).

The RIFLE classification was used in this study to identify patients with AKI.

2.1.6.5 Central nervous system function

The brain plays a pivotal role in sepsis, acting as both mediator of the immune response and a target for the pathologic process. The measurement of brain dysfunction is difficult because there are no specific biomarkers of neuronal injury, and bedsides, evaluation of cognitive performance is difficult in the ICU. Altered mental status is present in up to 23% of patients with sepsis. When, present, sepsis-associated encephalopathy (SAE) is associated with poor prognosis (44).

The pathophysiology of SAE involves direct cellular damage to the brain, mitochondrial and endothelial dysfunction, disturbances in neurotransmission and derangements of calcium homeostasis in brain tissue. Cerebral blood flow may also be affected. TNF-α appears to be the most significant inflammatory mediator involved in SAE (44).

2.1.6.6 Circulatory function

Significant derangement in autoregulation of circulation occurs in sepsis. Vasoactive mediators cause vasodilatation and increase microvascular permeability at the site of infection. Nitric oxide (NO) plays a pivotal role in the vasodilatation of septic shock. The secretion of vasopressin may be impaired, resulting in persistent vasodilatation Changes in both systolic and diastolic ventricular performance occur in sepsis. Cardiac output often increases to maintain blood pressure in the presence of systemic vasodilatation (12, 45).

The microcirculation consists of arterioles, terminal arterioles, capillaries, and post-capillary and collecting venules. The most important function of the microcirculation is the regulation and distribution of flow within the different organs. In septic shock, microcirculatory dysfunction may arise as a result of endothelial dysfunction, leukocyte-endothelium interactions, coagulation, inflammatory disorders and hemorrheologic abnormalities (46).

The major cell types constituting microcirculation include endothelial cells lining (ECL) inside of the microvessels. These form the interface between the circulating blood and the parenchymal cells responsible for organ function. They are critical for the regulation of haemostasis, vasomotor control and immunological function. The endothelium forms part of the essential vascular barrier for solute transport and osmotic balance. Sepsis is associated with severe endothelial cell dysfunction leading to dysregulation of haemostasis and vascular reactivity as well as tissue oedema. The glycocalyx is a 0.2 to 0.5 µm-thick gel-like layer lining the luminal membrane of the ECL. Glycocalyx shedding occurs in sepsis and other disease states owing to the presence of hyperglycaemia, cytokines, oxidants and bacterial endotoxins. The main instigators for glycocalyx shedding are thought to be reactive oxygen species (ROS), as well as TNF-α and heparinase. Loss of barrier function induced by glycocalyx shedding is associated with the formation of oedema and contributes to sepsis-induced organ failure (45).

2.1.7 Nutritional consequences of sepsis

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 (2).

During the early post-injury phase, energy expenditure (EE) is usually lower than before injury and during the later phases, it increases. Hypermetabolism is induced by signals from stress hormones, inflammatory cytokines, and other mediators. To meet the energy demand related to hypermetabolism, the body turns to its endogenous energy sources, namely glucose, by gluconeogenesis in the liver, and free fatty acids, by lipolysis in the adipocytes. The oxidation of carbohydrates (CHO) is increased more during the early phase than the oxidation of lipids and proteins. Glucose is the preferred energy substrate. Changes in the metabolism of CHO include the rapid utilisation of the glycogen stores, followed by a high level of endogenous glucose production from lactate, glycerol and alanine in the liver, kidney and intestine. As the turnover of glucose is increased, plasma concentrations of glucose will increase, resulting in stress hyperglycaemia (2, 20).

Later on, glucose utilisation is decreased with an increased fat turnover, and loss of muscle and visceral protein mass. Endogenous triglycerides (TGs) stored in the adipose tissue and exogenous TGs released from chylomicrons and other lipoproteins are avidly hydrolysed to release free fatty acids (FFAs) and glycerol into the bloodstream during critical illness, regardless of the amount of exogenous lipids provided. FFAs are converted to ketone bodies or re-esterified to TGs and

released into the bloodstream as very-low-density lipoproteins (VLDL), which are subject to impaired clearance. Plasma FFA levels are increased in critically ill patients over the first few days. The metabolism of lipids is increased, although complete oxidation can only be achieved in tissues where mitochondria are functional (2, 5, 20).

A negative nitrogen balance is the result of an increased protein breakdown over protein synthesis. This occurs even when reprioritisation leads to an increased overall hepatic protein synthesis. The amino acids released during the degradation of proteins will be either re-used by the gluconeogenesis organs or oxidised and will provide urea and ammonium as waste products. Plasma amino acids generated from increased skeletal muscle proteolysis also contribute to glucose production in the liver. Consequently, the skeletal muscles will be rapidly depleted. These losses are related to the significant wasting of muscles involved in ICU-acquired muscle weakness (2, 47).

2.1.8 Management of sepsis

Current management aims to control infection, to achieve haemodynamic stabilisation, to modulate the immune response and to provide organ and metabolic support, by treating the source and providing adequate oxygen delivery, ensuring glucose control and nutrition support (27).

The control of the infection relies on two components: removal of the infected focus and appropriate antimicrobial therapy. The infected focus must be identified by repeated clinical examination and available imaging techniques, and removed with surgical intervention when necessary. All appropriate cultures should be taken before microbial therapy is started (32). Prompt and effective treatment of the active infection is essential to the successful treatment of sepsis and septic shock (19).

Haemodynamic stabilisation can be separated into two key components: administration of fluids and use of vasoactive agents to counteract vasoplegic shock (27). According to the new Surviving Sepsis Guidelines, fluid resuscitation should be initiated as soon as possible. They recommend that, in the resuscitation from sepsis-induced hypoperfusion, at least 30ml/kg of intravenous (IV) crystalloid fluid be given within the first 3 hours. Additional fluids should be guided by frequent assessment of haemodynamic status as well as normalising lactate levels. They suggest that dynamic (passive leg raise, variations in systolic and pulse pressure or stoke volume) over static variables be used to predict fluid responsiveness where available. They recommend an initial target MAP of 65 mm Hg in patients with septic shock requiring vasopressors. Norepinephrine is the vasopressor of choice (48).

Metabolic support with the use of corticosteroids in patients with severe sepsis has been a controversial subject in recent years. The Surviving Sepsis Guidelines advise against the use of IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor

therapy are able to restore haemodynamic stability. If this is not achievable, a dose of 200mg/day of IV hydrocortisone is recommended (19, 48).

Protocolised glucose control may result in improved survival rate. The Surviving Sepsis Guidelines recommend a protocolised approach to blood glucose management in ICU patients with sepsis. Insulin dosing should commence when two consecutive blood glucose levels are >10mmol/L. This approach should target an upper blood glucose level ≤10mmol/L. Blood glucose values should be monitored every 1 to 2 hours until glucose values and insulin infusion rates are stable, then every 4 hours thereafter (48).

Nutrition support is important in all critically ill patients. The enteral route is preferable and should be commenced once initial resuscitation and adequate perfusion pressure is achieved. Where enteral feeding is impossible or not tolerated, parenteral nutrition (either as total or supplementary) may safely be administered (49).

2.2 Nutritional therapy in the critically ill patient

In this literature review, nutrition therapy in general is not discussed. The main focus is on parenteral nutrition and the components pertinent to this research. Thus, the focus is on intravenous lipid emulsions, particularly fish oil and their immunomodulatory role. As some of the parenteral nutrition available in South Africa is compounded by a facility and provides complete parenteral nutrition, including glutamine and micronutrients, the immune modulatory roles of glutamine and antioxidants are also included.

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 feeding intake that accompanies severe illness (50). Recent research indicates that critically ill or major surgical patients can lose as much as a kilogram of lean body mass (LBM) a day, much of it in the first week of ICU stay. Patients may gain weight back post ICU, but much of the weight gain is fat mass, not functional lean muscle mass (14).

2.2.1 Goals of nutrition therapy

Nutritional needs in the critically ill are poorly understood and vary with the phase of critical illness. Goals of nutrition therapy (NT) focus on attenuating the metabolic response to stress, preventing oxidative cellular injury, and favourably modulating the immune response (16). This includes providing adequate nutrition therapy, preventing any nutritional deficiencies, preserving lean body mass, maintaining glucose control, avoiding metabolic complications, decreasing infectious complications, and improving clinical outcomes (8).

2.2.2 Malnutrition

The incidence of malnutrition in hospitalised patients on admission is about 15–70%. It has been reported that approximately 70% of malnourished patients remain undiagnosed. These patients often enter and leave the hospital without receiving any nutritional therapy (51). Critically ill patients are at increased risk for the development of malnutrition due to alterations in protein and (52) energy metabolism displayed in response to sepsis, burns, major surgery and trauma. Malnutrition in critically ill patients includes both underweight and overweight patients, and body mass index (BMI) is used to classify these patients. An underweight patient has a BMI <18.5 kg/m^2 and an overweight patient has a BMI between 25 and 29.9 kg/m^2. Patients are classified as obese if the BMI is between 30 and 39.9 kg/m^2, and morbidly obese if the BMI ≥40 kg/m^2 (53). It is estimated that 25–30% of patients admitted to an ICU have a BMI >30 kg/m^2 (54). Malnutrition is associated with increased cost of care and poor patient outcomes, including nosocomial bloodstream infections, pressure ulcer development and increased mortality (55).

The risk of malnutrition identified on admission and the worsening of nutritional status during hospitalisation have been strongly associated with prolonged length of stay. These patients are more likely to be readmitted and their cost of treatment 20% higher than the average patient (55).

In 2015, the European Society of Clinical Nutrition and Metabolism (ESPEN) published a consensus statement on the diagnostic criteria for malnutrition. See Table 2-6 (56).

Table 2-6 : Diagnostic criteria for malnutrition(56)

- BMI <18kg/m^2

  or

- Unintentional weight loss >10% indefinite of time or >5% over the last 3 months combined with either

  BMI <20kg/m^2 if < 70 years of age, or <22kg/m^2 if ≥ 70 years of age or

  fat-free mass index <15 and 17 kg/m^2

Alberda et al. examined the relationship between the amount of energy and protein received and clinical outcomes, i.e., 60-day mortality and ventilator-free days (VFD) and explored how nutritional status prior to ICU admission modifies this relationship. Specifically, patients with a poor nutritional status, demonstrated by a low BMI, were more likely to experience adverse effects from underfeeding or benefit the most from receiving an increased amount of energy and protein. They concluded that critically ill patients with a BMI of <25 or ≥35 kg/m^2 had improved clinical outcomes with increased energy and protein intakes (57).

2.2.3 Nutritional risk assessment

Nutritional status assessment is performed to classify nutritional status, identify nutritional risk and to serve as a baseline for monitoring nutrition support adequacy. Identification of nutritional risk indicates the need for nutrition therapy to maintain body functions and to facilitate recovery (51). Recently, the NUTrition Risk in the Critically ill (NUTRIC score) was validated for nutritional risk assessment and identifies patients that benefit from higher nutritional intake. Patients with a low NUTRIC score (0–5) predict low malnutrition risk, and high scores (6–9) identify patients with increased ventilation duration and mortality (58). However, in the Brazilian population, the NUTRIC score didn't identify high-risk patients; the average score was only 4; however the overall hospital mortality was 38%. Thus the NUTRIC score failed to identify critically ill patients most likely to benefit from optimal amounts of macronutrients (59). This score has not been validated in the South African population.

The Nutritional Risk Screening (NRS) tool 2002 was developed by ESPEN for hospitalised patients to help identify which patients would benefit from nutrition support (60).

Table 2-7: NRS 2002 (61)

Impaired nutritional status		Severity of disease	
Score		Score	
Mild: 1	Weight loss >5% in 3 months or food intake below 50–75% of normal requirement	Mild: 1	Hip fracture, chronic patients, in particular with acute complications: cirrhosis, COPD, chronic dialysis, diabetes, oncology
Moderate: 2	Weight loss >5% in 2 months or BMI 18.5–20.5 + impaired general condition or food intake 25–60% of normal requirement	Moderate: 2	Major abdominal surgery, stroke, severe pneumonia, hepatologic malignancy
Severe: 3	Weight loss >5% in 1 months or BMI <18.5 + impaired general condition or food intake 0–25% of normal requirement	Severe: 3	Head injury, bone-marrow transplantation, intensive-care patients (APACHE >10)
Score (nutritional status) ☐ + Score (disease severity) ☐ = Total score ☐ Adjustment for age: if ≥ 70 years: add 1 to total score above Age adjusted score ☐			

Abbreviations: BMI: Body Mass Index, APACHE: Acute Physiology and Chronic Health Evaluation, COPD: Chronic Obstructive Pulmonary Disease

Refeeding syndrome could occur in malnourished and many ICU patients who have been nil per os for longer than 24 – 48 hours, when nutritional support is instituted (58). (See Table 2-8.) Potentially fatal shifts of fluids and electrolytes occur, especially hypophosphataemia, hypomagnesaemia, hypokalaemia, thiamine deficiency and changes in blood glucose, protein and fat metabolism. It is important to identify the patients that are at risk and monitor them closely (51).

Table 2-8: Patients at risk from refeeding syndrome (62)

- Anorexia nervosa
- Chronic alcoholism
- Oncology
- Postoperative
- Elderly
- Uncontrolled diabetes mellitus
- Chronic malnutrition
  - Marasmus
  - Prolonged fasting or low-energy diet
  - High-stress patient underfed for > 7 days
  - Malabsorption syndromes
- Long-term users of antacids
- Long-term users of diuretics

2.2.4 Parenteral nutrition

Parenteral Nutrition (PN) is the intravenous administration of macronutrients and micronutrients (63). The timing of initiating PN as well as the amount to be delivered differs depending on which guidelines are followed. See Table 2-9 below discussing the differences between the ASPEN, Canadian and ESPEN guidelines. The British Association for Parenteral and Enteral Nutrition (BAPEN) recommends that PN should be used to prevent or treat malnutrition when the intestine is unavailable, or the intestinal function is inadequate. Treatment should be initiated before malnutrition has developed and the nutrient prescription should reflect the estimated nutritional requirement and patient's clinical condition. The administration of nutrients in excess of estimated need is wasteful and potentially dangerous. These recommendations do not specify the exact timing of initiating PN (64). The South African National Parenteral Nutrition Practice Guidelines for Adults suggest to start PN as soon as possible post admission, in patients who are not expected to tolerate <60 % of their oral or enteral nutrition (EN) by day 3 to 5. They also recommend early nutrition intervention and introduction of PN in patients with pre-existing malnutrition (65).

Table 2-9: Published recommendations for indications and initiating PN from different societies

Recommendations	ASPEN (66)	Canadian (67)	ESPEN (68)	SA National PN Guidelines (65)
Indications and initiation of PN	Withhold exclusive PN over the first 7 days following ICU admission if the patient has a low nutrition risk (NRS 2002 ≤3 or NUTRIC score ≤5) and EN is not feasible. If the patient has a high nutrition risk (NRS ≥5 or NUTRIC score ≥5) or is severely malnourished, and EN is contraindicated, PN needs to be initiated as soon as possible following ICU admission. The use of supplemental PN (SPN) should be considered after 7–10 days in patients with either low or high nutrition risk, if they are unable to meet >60% of energy and protein requirements by the enteral route alone.	In critically ill patients with an intact GIT, it is recommended that PN not be used routinely. Early PN should be considered in nutritionally high-risk patients, with a relative contraindication to early EN. For critically ill patients starting on EN we recommend that PN not be started at the same time as EN. There is insufficient data to recommend when to start PN when patients are not tolerating EN.	Patients should be fed because starvation or underfeeding is associated with increased morbidity and mortality. PN should be initiated within 24–48 hours if ICU patients are not expected to be on normal nutrition within 3 days and EN is contraindicated or they cannot tolerate EN. All patients receiving less than their targeted enteral feeding after 2 days should be considered for SPN.	Recommend early nutrition intervention and introduction of PN in patients with pre-existing malnutrition. Start PN as soon as possible post admission, in patients who are not expected to tolerate <60 % of their oral or EN by day 3 to 5.

Abbreviations: PN: Parenteral Nutrition, NRS: Nutritional Risk Screening, NUTRIC: Nutrition Risk in the Critically ill, EN: Enteral Nutrition, ICU: Intensive Care Unit, ASPEN: American Society of Parenteral and Enteral Nutrition, ESPEN: European Society of Clinical Nutrition and Metabolism.

There are considerable differences in terms of timing of initiating PN and this is particularly owing to the differences between the target populations, the levels of evidence considered, the clinical recommendations put forward, as well as the different types of parenteral nutrition products registered and available for use in the various countries (69). All the guidelines agree when the patient is malnourished or at high risk, PN should be initiated as soon as possible following ICU admission.

See Table 2-10 for circumstances where PN is the preferred method of nutritional therapy

Table 2-10: Indications for PN (63, 65, 70)

Indications	Clinical features
Prolonged ileus > 3 days	Generalised peritonitis Peritoneal metastatic cancer Abdominal distension on EN 'Frozen abdomen' with chronic obstructive symptoms Acute abdomen
Short bowel syndrome	Massive small bowel resection leaving <1.5m Mesenteric infarction Intestinal atresia
Mechanical bowel obstruction	Intrinsic or extrinsic blockage of intestinal lumen
Severe malabsorption	Radiation injury to the intestine High output fistulae (>500ml per 24h) Inflammatory bowel disease in acute phase Splanchnic ischaemia Complications of bariatric surgery
Time to reach full EN or oral intake > 5 days	Inability to provide sufficient nutrients enterally Inability to obtain enteral access
Malnutrition	With a non-functioning GIT
Hyperemesis gravidarum	When nausea & vomiting persists for 5–7 days and EN is not possible
High risk of aspiration	Intractable vomiting
High-dose chemotherapy	With severe mucositis
Need to restrict oral or enteral intake	Severe pancreatitis Chylous fistula Trauma requiring repeat surgical procedures and lengthy period of nil per os status

Complete PN in its modern form was invented by Arvid Wretlind and colleagues in Sweden and the USA in 1961. This feeding technique enabled patients with compromised GI failure to receive nutrition support and ultimately saved the lives of many previously doomed to die. Since the start of this new feeding technique, PN has evolved and the way we prescribe it has changed; however it has generated numerous contradictory publications. In the 1970s and 1980s the observation of extensive loss of lean body mass led to the rationale for feeding large glucose loads, thought to suppress endogenous gluconeogenesis, thereby preventing amino acid loss. This was known as hyperalimentation and resulted in overfeeding, dextrose intake exceeding the body's ability to oxidise glucose resulting in increased infectious complications, CO_2 overproduction, increased O_2 consumption, and increased adrenaline and noradrenaline release, compared with EN. The awareness of the importance of controlling blood glucose levels only came to the forefront in 2001 and changed how patients are managed in the ICU. Today the production of metabolically balanced amino acids, different types of lipid emulsion (LE), lower glucose content with a lower NPE:N ratio, micronutrients and trace elements have made PN a safe alternative form of NT where EN is contraindicated (63).

Doig et al. compared early PN in critically ill patients with short-term relative contraindications to early EN. A total of 1372 patients were randomised to receive either standard of care (commencement of EN or PN in 2.8 days) or early PN commenced within 44 minutes after enrolment. Day-60 mortality did not differ significantly. The early PN strategy resulted in significantly fewer days of invasive ventilation but no significantly shorter ICU or hospital stay (71). In a full economic analysis of this trial, the early PN strategy reduced total cost of acute hospital care by US$3150 per patient (72).

In a meta-analysis of 18 RCTs comparing enteral with parenteral nutrition in ICU patients, no overall mortality difference was found, but fewer infections were reported with EN. This effect was more pronounced when the PN group received more calories, whereas no effect was seen with similar caloric intake, suggesting that overfeeding by PN is associated with more infections (73).

2.3 Nutritional requirements

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.

2.3.1 Energy

Accurate determination of energy requirements in the critically ill is difficult. Firstly, resting energy expenditure is highly variable during the course of critical illness owing to changes induced by shock, sedation, surgical procedures, temperature, ventilation, physiotherapy, mobilisation and loss of LBM (63). Secondly, accurate determination of energy targets requires knowledge of pre-

illness weight and body height, data which is often missing. Thirdly, actual body weight is frequently inaccurate owing to fluid accumulation post resuscitation (74), while dry weight is a poor indicator of LBM, especially in the obese patient where body weight is increased by excess fat mass (63, 75).

Indirect Calorimetry (IC) remains the gold standard for predicting energy requirements. However, this method is fairly expensive, time-consuming and remains unavailable in most ICUs (63, 76). Predictive equations are therefore frequently used as surrogates to estimate energy requirements. Most of these were developed for use in the healthy population and there is currently no consensus as to the most accurate equation for estimating energy requirements in the critically ill patient (77). The following equations: Harris–Benedict, Mifflin, Owen, the American College of Chest Physicians (ACCP), Ireton-Jones 1992 and 1997, Penn State 1998 and 2003, and Swinamer 1990 are most commonly used. However, the results from these correlate poorly with those of IC (75). The most significant source of error in these equations is the use of estimated, rather than measured weight (77). Berger and Pichard suggest that the Toronto equation for major burns and the Faisy–Fagon equation for patients on mechanical ventilation were developed specifically for critically ill patients and are clinically more accurate than other predictive equations for metabolically stable, mechanically ventilated patients (75).

The last method for determining energy requirements is the use of a fixed daily prescription, usually in the range of 20–35kcal/kg (76,77). Despite the greater ease of applying this method at the patient's bedside, accuracy is generally regarded as poor. Accuracy might be improved by using metabolically active weight, but currently there is no reliable definition of metabolically active weight (77). A number of professional organisations and authors have developed consensus guidelines for the determination of nutritional requirements in critical illness (see Table 2-11).

Additional energy provided by dextrose-containing fluids and lipid-based medications such as propofol and citrate dialysis should be accounted for when deriving NT regimens to meet target energy goals, to avoid overfeeding (58,66). In a recent publication by Veldsman et al., the non-nutritional energy sources, mostly from carbohydrate-containing IV fluids, contributed 8% to total energy delivery (78).

Overfeeding can occur easily with PN, especially during the first 2–3 days in the ICU. During this initial acute phase of critical illness, endogenous energy sources are utilised to meet total energy expenditure. The utilisation of exogenous energy sources is limited, and even administering a large amount of energy will not terminate this response. Thus, introducing early full feeding will create overfeeding which is associated with poor outcome and increased mortality. Potentially deleterious effects of overfeeding early are hyperglycaemia, hyperlipidaemia and hypercapnia, resulting in increased infectious complications and liver steatosis (14, 79).

During the later chronic or recovery phase of critical illness, the body experiences a massive increase in metabolic needs, with total energy expenditure increasing as much as ~1.7 fold above resting energy expenditure (14).

Table 2-11: Published guidelines for nutrient intake in critically ill patients requiring PN

Society	Year	Energy (kcal/kg/day)	Protein (g/kg/day)
ACCP (80)	1997	25	-
CCCPG (67)	2015	No recommendation (insufficient evidence)	No recommendations for protein **Glutamine**: When PN is prescribed to critically ill patients, we recommend parenteral supplementation with glutamine not be used
ESPEN (68)	2009	25 if IC not available (Grade C)	1.3–1.5 (+0.3-0.6 alanyl-glutamine dipeptide) (Grade A)
ASPEN (66)	2016	25 – 30 or predictive equations if IC not available **Obesity:** 60–70% of energy requirements or 11–14 (actual BW) 22–25 (IBW) **PN:** 20kcal/kg/day or 80% of estimated energy needs, for first week in ICU	1.2–2.0 **Obesity:** ≥ 2 (IBW) (BMI 30–40) ≥2.5g (IBW) (BMI ≥40) > 1.2 **Glutamine:** Parenteral glutamine supplementation not be used routinely in the critical care setting
SA National DoH PN Guidelines (65)	2016	20–25 (acute phase) 25–30 (recovery phase) **Obese (BMI>30)** Hypo-caloric feeding: 11–14 actual BW Eucaloric feeding: 21 actual BW	1.3–1.5 **Obese (BMI>30)** ≥ 2 (IBW) (BMI 30–40) ≥2.5g (IBW) (BMI ≥40)

Evidence grades: B, supported by at least one well-designed randomised controlled trial or other sound methodology; C, based on expert opinion or advice.

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; IC: Indirect Calorimetry; IBW: Ideal Body Weight; BMI: Body Mass Index; BW: Body Weight; ICU: Intensive Care Unit

The Tight Calorie Control Study (TICACOS) investigated whether indirect calorimetry-based feeding is superior to equation-based feeding (target 25kcal/kg/day). IC was performed throughout ICU stay and was repeated every 48h. Although the primary end point (hospital mortality) was not statistically different, morbidity was increased in the IC group, which received approximately 600kcal/day more. The increased calories provided could likely explain the observed increased incidence of pneumonia and prolonged ventilation (50).

The Early Parenteral Nutrition to supplement insufficient enteral nutrition in ICU patients (EPaNIC) trial randomised patients on admission to early (day 2) versus late (day 8) PN and concluded that early hypercaloric PN is deleterious (81). Overfeeding leads to increased insulin requirements to achieve blood glucose control. The patients in the early PN group in the EPaNIC trial needed nearly double the amount of insulin for this purpose, probably reflecting overfeeding that is associated with depressed autophagy (63, 75).

The SPN trial showed that individualised energy supplementation using IC from day 4 in ICU could reduce nosocomial infections and should be considered as a strategy to improve clinical outcome in patients in the ICU for whom EN is insufficient (82). Grau and colleagues have shown liver dysfunction during artificial nutrition support, especially TPN, occurs more frequently if energy delivery exceeds 25kcal/kg, and in patients with sepsis (83).

McCowen and colleagues randomised adult patients requiring PN to either receive hypocaloric PN (1000kcal and 70g protein) and standard weight-based regimen PN (25kcal/kg and 1.5g protein/kg) for more than five days. They found that the provision of PN to a goal of 25kcal/kg and 1.5g protein/kg was not associated with more hyperglycaemia or infections, but provided significant nutritional benefit in terms of nitrogen balance in comparison with hypocaloric PN (84).

Whether measured by IC or estimated by predictive equations, energy expenditure should be re-evaluated more than once per week, and strategies to optimise energy and protein intake should be used (66).

Prolonged underfeeding may result in a cumulative energy and/or protein debt that cannot be compensated for later during ICU stay, resulting in increased infections and mortality (85-87). A large international survey indicated that ICU practitioners deliver an average of 59% of energy requirements, resulting in suboptimal NT (88).

In conclusion, each patient should be closely monitored for signs and symptoms of overfeeding, as well as feeding intolerance, and appropriate measures should be taken to avoid these complications. On the other hand, severe underfeeding can also be harmful and justifies continuous efforts to optimise nutrient delivery and feeding tolerance (89).

2.3.2 Protein

Critically ill patients can lose as much as a kilogram of LBM a day during the first week of ICU stay. It is most pronounced in skeletal muscle, where it is mediated through an increase in muscle protein breakdown. This increase in degradation rate is uniformly distributed among cellular proteins: contractile and mitochondrial (90). Depletion of muscle mass is associated with impaired function and poor outcomes (91). The International Protein Summit in 2016 suggested that high doses of protein in the range of 1.2 – 2.5g/kg/day may be required in the setting of the ICU to optimise nutrition therapy and reduce mortality. Protein doses in this range may be needed to best stimulate new protein synthesis and preserve muscle mass. They recommend that achieving protein goals the first week following ICU admission should take precedence over meeting energy goals (92).

Observational studies show higher protein intake is associated with better survival and more ventilator-free days (85, 93-95). See Table 2-11 on consensus guidelines for the determination of nutritional requirements in critical illness for protein intake recommendations.

An improvement in quality of life (QoL) linked with protein intake was explored in a recent publication by Wei et al. (96) in high-risk ICU patients, who were ventilated for > 8 days. Patients receiving low nutritional adequacy over the first ICU week (<50% of predicted calorie and protein need) had an increased mortality versus patients receiving high nutritional adequacy (>80% of calorie and protein needs). They also demonstrated that for every 25% increase in calorie/protein delivery in the first ICU week, there was an improvement in 3-month post-ICU physical QoL scores (as measured by the SF-36) with medical ICU patients showing significant improvements in both 3- and 6-month SF-36 scores. A recent publication by the Australian and New Zealand Intensive Care Society indicated that a 7.8 point change in physical QoL domain scores is considered clinically relevant in post-ICU patients. In the Wei study, there was a 10.9 point increase in physical functioning and a 13.1 point increase in role-physical measures, thus indicating the post-ICU QoL can improve significantly by just a 25% increase in calorie/protein delivery during the first 8 days of ICU stay (14, 96).

Another recent RCT by Ferrie et al. (97) investigated isocaloric nutrition with different amounts of a parenteral amino acid solution (1.2g/kg/day versus 0.8g/kg/day) in 119 critically ill patients requiring PN and measured handgrip strength as the primary outcome. The actual amino acid delivery was 1.1g/kg/day versus 0.9g/kg/day, averaged over the first 7 days. Grip strength at ICU discharge tended to be higher in the high amino acid group. This group showed less fatigue and greater forearm and thigh muscle thickness at day 7. At day 3, nitrogen balance was significantly improved in the high amino acid group, but this effect disappeared completely at day 7. There was no difference between groups in terms of mortality or LOS. They concluded that the higher level of amino acids was associated with small improvements in a number of different measures, supporting guideline recommendations for ICU patients (97).

There are also some negative reports on higher protein intake in ICU patients. In a post hoc analysis of the EPaNIC trial, it was suggested that higher protein intake at day 3 was related to worse clinical outcome (98). However, this analysis was likely not adjusted for energy intake (103). The investigators proposed that early high protein nutrition support was harmful because of inhibition of autophagy (98).

Puthucheary et al. (100) suggest that protein feeding might have adverse effects. However, this conclusion was based on two regression analyses, of which one indicated worst outcome and the other did not. There was no actual information in this report on intake, but it appears to be low (101).

While autophagy is an important maintenance instrument, it remains to be determined to what extent autophagy is suppressed by protein feeding and whether this may affect clinical outcomes. While this is an interesting hypothesis, it is unproven and other recent trials refute this concern (3, 102, 103).

Caution should be employed when prescribing high protein levels, and monitoring for clinical response may be required. The potential harm from excessive protein or amino acids is generally from the delivery of protein without adequate energy sources from CHO. Azotaemia will interfere with cellular protein synthesis only when the level of serum urea nitrogen becomes excessive. Clinically, serum urea nitrogen may be tempered as patients are given renal support therapy prior to reaching uraemia-inducing levels. Altered mental status can be observed from excessive amino acids, specifically the aromatic amino acids, as there is a deficiency of branch chain amino acids. It is the imbalance that causes hepatic encephalopathy in patients with compromised hepatic function (104).

2.3.2.1 Glutamine

Historically, it was difficult to include glutamine into amino acid solutions owing to stability and solubility problems. In the early 1990s, glutamine was finally solubilised as the dipeptide form glutamine-alanine and glycyl-glutamine. Glutamine is the most abundant free amino acid in the body, which constitutes over 60% of muscle free amino acid pool. Classified as a nonessential amino acid, glutamine can be produced in the body by conversion of glutamic acid, primarily by the skeletal muscle and liver. Glutamine has important physiologic functions, mainly serving as a precursor in the synthesis of other amino acids and glucose for energy. See Table 2-12 for all the physiologic functions of glutamine (63, 105).

The concept of conditionally essential amino acids emerged in the early 1990s; these are amino acids that are supplied by food and synthesised under normal conditions but which during critical illness become deficient because of insufficient supply and increased consumption. Isolation of various amino acids led to the possibility of using them separately, potentially as drugs (63).

Table 2-12: Physiologic functions of glutamine (106, 107)

- Precursor of arginine and nicotinamide adenine dinucleotide
- Antioxidant role; precursor of glutathione and attenuation of induced nitric oxide synthase activation after sepsis
- Oxidative fuel for rapidly proliferating cells, e.g. GIT, Immune system, reticulocytes and fibroblasts
- Anti-inflammatory/immune regulation by attenuating cytokine release and NF-κB activation
- Tissue protection:
    - Functions as a signal molecule and enhances stress-induced heat shock protein expression
    - Decreases cellular apoptosis
- Preservation of tissue metabolic function
    - Attenuates insulin resistance
    - Preservation of ATP levels following sepsis

Glutamine is naturally found in dietary protein and becomes conditionally essential under conditions of catabolic stress and critical illness. Demands of glutamine in critical illness are met in part by skeletal muscle proteolysis. The release of large amounts of glutamine to maintain normal concentrations in the plasma result in depletion of glutamine stores. Depletion of glutamine has been shown repeatedly to occur in critically ill patients; a low plasma glutamine level in the critically ill patient in ICU at the time of admission was found to be an independent predictor of mortality (108, 109).

Well-conducted repletion studies have shown that glutamine administration is beneficial if administered, particularly by the parenteral route, along with an optimised NT-improving glucose control and achieving reduction of both infectious complications and mortality (110, 111). But glutamine alone cannot be provided in standard PN for stability reasons, which increases the risk of deficiency (63).

A meta-analysis on the impact of perioperative glutamine dipeptide-supplemented PN in abdominal surgery patients showed a significant decrease in infectious complication rates, a reduction in hospital LOS, and a positive effect on nitrogen balance, but no effect on mortality in the glutamine group (112).

Bollhalder et al. conducted a meta-analysis of parenteral glutamine supplementation in critically ill patients and patients undergoing major surgery. The study showed a significant reduction in infections and a shorter length of stay, and a non-significant reduction in short-term mortality in the glutamine group (113).

Two large prospective randomised clinical trials caused confusion with regard to the use of glutamine in critical illness. The dose of glutamine as well as the timing of administration could explain the negative results (63). Andrews et al. enrolled 502 patients with gastrointestinal failure. The patients were randomised to receive daily 20.2g glutamine or 500µg selenium, or both, versus placebo for up to 7 days. There was no overall effect of glutamine on new infections or on mortality, while selenium was associated with less infectious complications if delivered for longer than 5 days. Several shortcomings of the study, including a very short administration time and a one-size-fits-all prescription of the ready-to-use 3-chamber PN bags, resulted in the delivery of a very low glutamine dose for a very short period (114).

Heyland et al. reports data for 1223 patients receiving the highest doses so far used for glutamine (0.78g/kg/day supplied as 0.35g/kg intravenously + 30g enterally per day), about twice the recommended doses, in patients with severe organ failure (93% of patients in shock and 33% with renal failure) starting within the first 24 hours of admission independently of nutrition. In addition, the glutamine group suffered more organ failure, which might explain on its own the higher mortality. Only 31% of a subset of patients presented with low baseline glutamine levels (<420µmol/l), whereas 15% of these patients had supranormal plasma glutamine values at baseline, which were associated with increased mortality. Pharmacological doses of glutamine in unstable patients should be avoided (115).

Subsequent to the above trials, there has been some data published on glutamine-supplemented parenteral nutrition still showing benefits. Grintescu et al. studied the influence of parenteral glutamine supplementation on glucose homeostasis in 82 critically ill polytrauma patients. They found that 63% of patients in the glutamine-supplemented group had no hyperglycaemic episodes and only 37% required exogenous insulin, with a mean lower dose than the controls. There was also a trend of fewer new infections in the glutamine group vs control group (10 vs 14) (116).

Chen et al. conducted a meta-analysis on glutamine therapy in critically ill patients. There was no significant difference in hospital and 6-month mortality between the glutamine group and the control group. However, in the high dosage subgroup (>0.5g/kg/day), the mortality rate in the glutamine group was significantly higher than that of the control group (33.5% vs 28.2%). The incidence of nosocomial infections in the glutamine group was significantly lower (117).

A recent meta-analysis by Stehle et al. (105) on glutamine-supplemented PN in critically ill patients confirmed a significant reduction in infectious complications (RR=0.70), ICU LOS (MD – 1.61 days), hospital LOS (MD – 2.3 days) and mechanical ventilation duration (MD – 1.56 days). It also lowered the hospital mortality rate by 45% but had no effect on ICU mortality. The authors conclude that supplementing PN with glutamine dipeptide according to ESPEN clinical guidelines as part of a

balanced nutrition regimen, significantly reduces hospital mortality, infectious complication rates and hospital LOS, and could also confer economic benefits in this setting (105).

Various societies have published consensus guidelines on the use of parenteral glutamine in critically ill patients. At present, the ESPEN guidelines state that when PN is indicated, the amino acid solution should contain 0.2–0.4g/kg/day of L-glutamine (0.3–0.6g/kg/day alanyl-glutamine dipeptide). However, the ASPEN guidelines recommend that parenteral glutamine supplementation not be used routinely in the critical care setting. According to Heyland and Dhaliwal, patients with shock and MOF should not receive glutamine; however for ICU patients not in MOF receiving PN, there is still a large body of evidence showing the benefit of IV glutamine at 0.35g/kg/day (118).

See Table 2-11 for the published recommendations on glutamine supplementation.

2.3.3 Carbohydrates

Carbohydrates (CHOs) are supplied as glucose. Cells such as red blood cells, immune cells and renal medullary cells which have no mitochondria are dependent on glucose supply for their energy through ATP production. Brain metabolism is also partially dependent on plasma glucose concentration: it can use lactate for energy supply when blood glucose decreases gradually (119) . Regarding other energy sources, our brain (unlike most of the other peripheral tissues) does not utilise fatty acids. Transported in the bloodstream bound to the albumin, fatty acids are unable to cross the haematoencephalic barrier (119). However, during long-term starvation, brain metabolism adapts to the consumption of ketone bodies (synthesised from the excess of acetyl-CoA). A full adaption develops approximately within three weeks of starvation. After this period, the brain is able to cover up to 50% of its energy expenditure from the oxidation of ketone bodies. Brain metabolism accounts for the majority of blood glucose oxidation in the body. It utilises around 20% of the total oxygen and 20% of the total glucose consumption (120). In the absence of an exogenous supply of glucose, the body can call upon hepatic glycogen stores and can synthesise glucose from lactate, lipids and amino acids through gluconeogenesis. Thus, an adequate supply of glucose is crucial to prevent wasting of amino acids as substrates for gluconeogenesis and thereby preserve body protein and muscle mass (123).

Glucose represents the only CHO source in PN and should always be infused with PN. The minimum glucose requirement for ICU patients is ≥2g/kg/day (65,68) or approximately 60% of non-protein energy (NPE) should be supplied as glucose with an intake of 3–3.5g/kg/day. In patients with a high risk of hyperglycaemia (critically ill, diabetes, sepsis or steroid therapy) an lower initial carbohydrate infusion of 1–2g/kg/day is recommended (121) .

Insulin resistance in the critically ill means that infusions of large amounts of glucose result in an increase in blood glucose levels. It has been documented that the maximum oxidation rate of glucose in the stressed patient is 4–7mg/kg/min (119). Hence, in order to decrease the risk of

metabolic alterations, the maximum rate of glucose infusion should probably not exceed 5mg/kg/min (68).

Excessive administration of glucose should be avoided because of the risk of hyperglycaemia with osmotic diuresis and hyperosmolar coma. Hyperglycaemia has pro-inflammatory effects, and worsens outcomes in critically ill patients. Target blood glucose levels should be kept between 7 and <10mmol/L for the general ICU population (66). Hypoglycaemia with PN is typically seen when endogenous insulin levels are not adjusted to abrupt withdrawal of dextrose, decreased dose of corticosteroids or vasopressors, or recovery from acute illness. It has also been associated with increased risk of complications, length of hospitalisation and mortality (122, 123).

Excess glucose is converted to fatty acids (FA) and stored in adipose tissue or in the liver, resulting in steatosis. Furthermore, glucose oxidation is associated with a high production of carbon dioxide which could increase respiratory stress (123).

2.3.4 Lipids

Intravenous lipid emulsions (LEs) provide a source of essential fatty acids (EFAs) and serve as a complement to carbohydrates by providing a dense source of NPE in PN. This is known as the Dual -Energy system. Lipids provide 9kcal/kg as a source of calories. Thus, fluid volume of PN required to achieve adequate caloric intake can be reduced substantially by adding lipids. LEs also have a low osmolarity and incorporating them into PN solutions can reduce the overall osmolarity of the solution and enable some solutions to be administered peripherally (≤900mOsm/L) or centrally (124).

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) (10, 124). Fatty acids (FAs) 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 (124, 125). Changing the FA composition of cells involved in the inflammatory response influences their functions. The anti-inflammatory effects of marine n-3 PUFAs suggest that they may be useful as therapeutic agents in disorders with an inflammatory component (126).

The metabolites of n-3 polyunsaturated fatty acids (PUFAs), 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 n-3 PUFAs 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 (37, 127). See Figure 2-1.

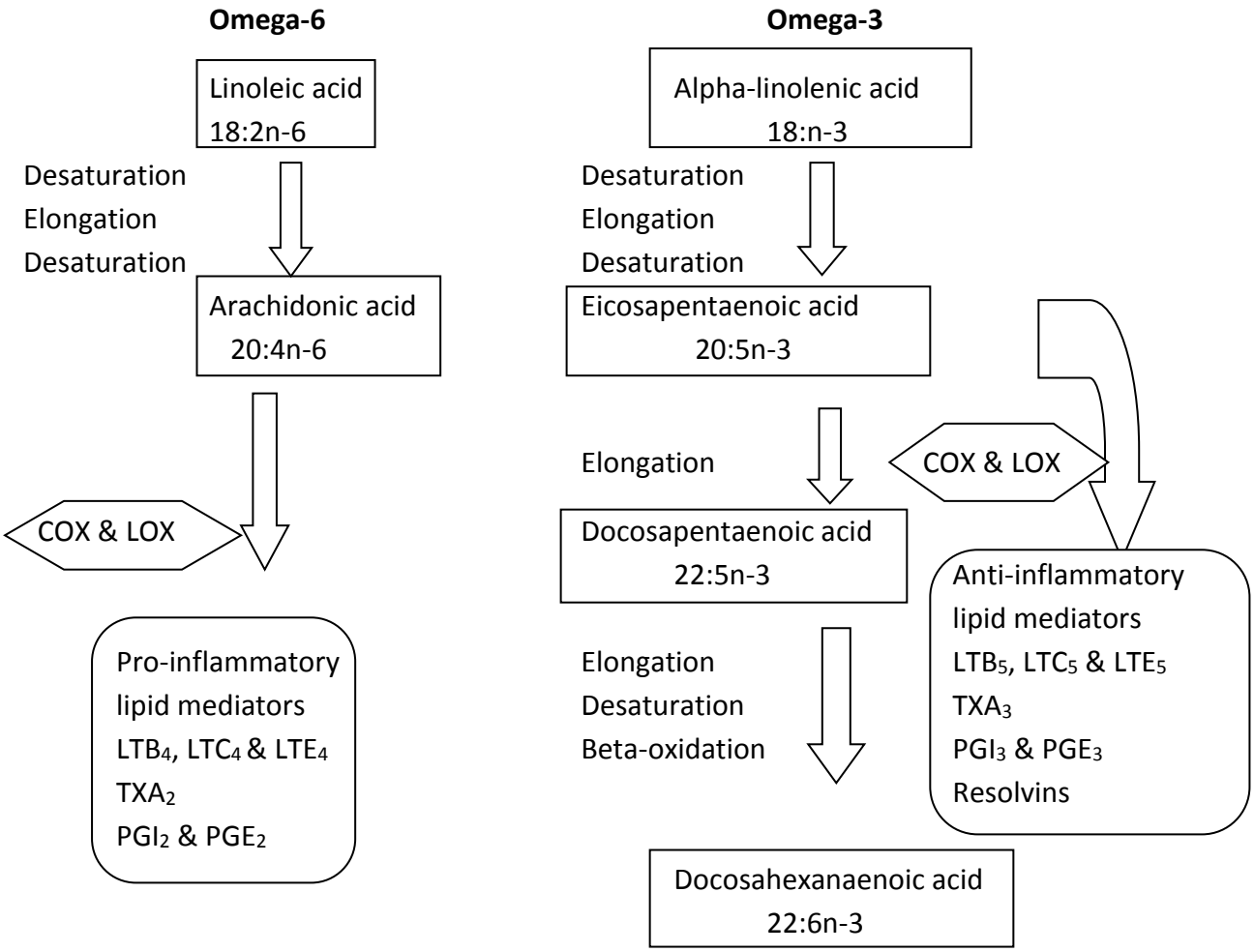

Figure 2-1: Metabolism of omega-6 and omega-3 PUFAs (adapted from (31, 37, 127)

COX – Cyclooxygenase, LOX: Lipoxygenase, TXA_2: Thromboxane A_2 (platelet aggregator, vasoconstrictor), PGI_2: Prostaglandin I_2 (vasodilator, antiaggregator), PGE_2 : Prostaglandin E_2 (Immunosuppresor)

Difference between Intravenous Lipid Emulsions (IVLEs)

The first LE that met the criteria for safe use as part of PN in the clinical arena was based on soybean oil (SO). This emulsion, named Intralipid®, was developed in 1961 in Sweden by Arvid Wretlind after numerous attempts to infuse lipids in humans for therapeutic purposes had failed. 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.. However a potential disadvantage with SO LEs is their high content of n-6 polyunsaturated fatty acids (PUFAs) . The emergence of evidence suggesting that n-6 PUFAs are pro-inflammatory and immunosuppressive has led to the development since the mid-1980s of the next-generation LEs based on various oil sources (10, 11). See Figure 2-2.

Despite sharing several common properties, the oil sources used and the percentages of different FAs dictate the key differences between IVLEs. Their differences account for their additional benefits or detrimental effects, especially when used for prolonged periods (see Table 2-13 for the analysis of LEs). Typically IVLEs are manufactured with 1 of 5 types of oil: soybean, safflower, coconut, olive or fish. Each has unique inflammatory properties and may even confer different pharmaceutical and therapeutic benefits (125).

Soybean oil

Soybean oil (SO) lipid emulsions remain the most widely used in many countries because of their proven record of safety and tolerability (10,11). SO contains high concentrations of n-6 PUFAs with a ratio of LA to ALA of approximately 7:1. LA is metabolised into AA. The eicosanoids generated from AA are prostaglandin E_2 (PGE_2), thromboxane A_2 (TXA_2) and leukotrienes, including LTB_4, which act in a pro-inflammatory way (Figure 2-1). 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 dysfunction (IFALD). The role of phytosterols in hepatocyte damage has been demonstrated by their antagonising effect on the farnesoid X nuclear receptor, which is critical in regulating the level of intrahepatic bile acids. In addition, the incorporation of phytosterols in erythrocyte membranes accelerates the breakdown of these cells and increases the bilirubin load to the liver (125).

Emulsions with a high content of n-6 PUFAs have been linked to immunosuppressive effects (128, 129). 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 an SO LE compared with those receiving lipid-free PN (130). This is the reason why many centres do not administer 100% SO LE to critically ill patients (125).

Safflower oil

Safflower oil has been used in IVLE alone or in combination with SO in the US since 1980. It was developed as an alternative to SO LE. In comparison with SO LE, safflower-based IVLE had higher concentrations of LA and less ALA. The use of safflower oil predisposed patients to develop n-3 PUFA deficiency when used as a sole source of fat in IVLE (125).

Coconut oil (MCTs)

Second-generation LEs consisted of the addition of medium-chain triglycerides (MCTs) to SO. It contains a 50/50 mixture. These emulsions reduce the n-6 PUFA content by 50%. MCTs are SFAs that are 6–12 carbons long and include caprylic, caproic and myristic 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 preferential 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 (9, 125).

Olive oil

Olive oil (OO) is rich in n-9 FA (oleic acid) a type of MUFA that is not considered essential. OO-based emulsions were introduced in Europe in the 1990s and are classified as third-generation IVLEs. The relatively small amount of LA explains why this oil source requires blending with an oil containing EFA, like SO. Olive oil has a lower content of phytosterol than pure SO. One OO-based LE is composed of 4 parts OO/1 part SO (ClinoOleic), thus providing 30% of the PUFA content of standard SO LE. In comparison to SO, OO is rich in MUFAs that possess fewer pro-inflammatory properties and are more resistant to oxidative stress injuries from free radicals (125, 127).

Fish oil

Fish oil (FO)-based LEs are the most recent developments as alternatives 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 oil (25%) and fish oil (15%) (SMOFlipid®). Mixing four different oils optimises the fatty acid profile and the n-6:n-3 PUFA ratio of 2.5:1 which is in accordance with current recommendations. (131).

Owing to the high concentrations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (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 FAs (127, 132).

Omega 6: omega 3 polyunsaturated fatty acid ratio

In an experimental immunocompetence model, Grimm et al. demonstrated that IVLEs show varying immunomodulatory effects dependent on the n-6:n-3 PUFA ratio. The optimum immune response was maintained by infusion of a lipid emulsion with an n-6:n-3 PUFA ratio of 2.1:1 (133). According to recommendations, new lipid emulsions should be composed of a reduced n-6 PUFA, especially linoleic acid, counterbalanced by MCT, MUFA and long-chain n-3 PUFA . Based on experimental and clinical studies, the most favourable n-6:n-3 PUFA ratio is proposed to range between 2:1 and 4:1 (11, 133-135).

Figure 2-2: Evolution of fat sources in intravenous lipid emulsions and their corresponding changes in the inflammatory profile (9, 125, 127)

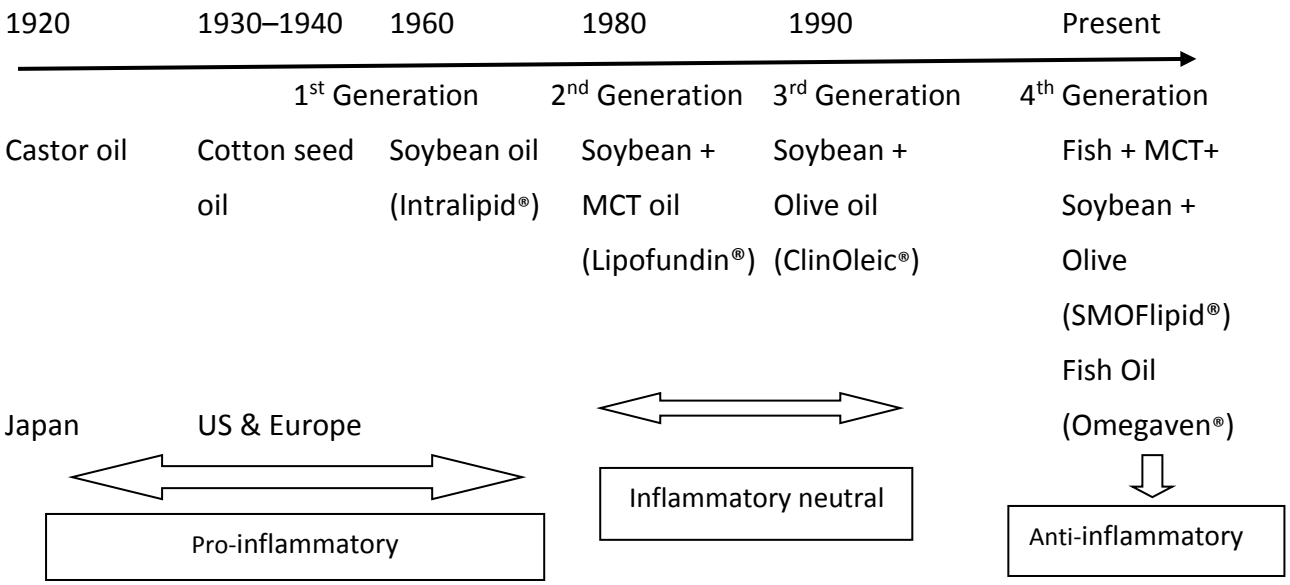

Table 2-13: Characteristics of commercially available intravenous lipid emulsions used In reported randomised controlled trials (9, 124, 125, 127, 136, 137)

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	3.0-4.7	19.2	3.5-3.7
DHA	0	0	0	2.0-4.4	12.1	2.5
n-6 – n-3 PUFAratio	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) Xu(142)	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; LCT: Long-Chain Triglyceride; MCT: Medium-Chain Triglyceride; OO: Olive oil; FO: Fish oil; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; SMOF: soybean, MCT: olive, fish

2.3.4.1 Guidelines on the use of lipids in PN

Various professional organisations have developed consensus guidelines for prescribing different types of lipids in PN (Table 2-14). These guidelines vary in terms of their recommendations according to the types of lipids available and registered in the various countries. Up 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.

Table 2-14: Published guidelines for different types of lipids in PN

Society	Year	Recommendation
ESPEN (68) (139)	2009	**ICU**: Lipid emulsions should be an integral part of PN for energy and to ensure EFAs provision in long-term ICU patients. IVLE (LCT, MCT or mixed emulsions) can be administered safely at a rate of 0.7g/kg up to 1.5g/kg over 12 to 24 hours. Addition of EPA and DHA to lipid emulsions has demonstrable effects on cell membranes and inflammatory processes. FO-enriched lipid emulsions probably decrease length of stay in critically ill patients.
	2017	**Surgery**: Postoperative PN including omega-3 PUFAs should be considered.
CCPG (67)	2015	When PN with IVLEs are indicated, consider IVLEs that reduce the load of omega-6 fatty acids/soybean oil emulsions. Insufficient data to make a recommendation on the type of lipids to be used that reduce the omega-6 fatty acid/soybean oil load in critically ill patients receiving PN.
ASPEN (66)	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 we cannot make a recommendation at this time owing to lack of availability of these products in the US.
SA National DoH PN Guidelines (65)	2016	0.7–1.5g/kg/day Essential FA: 7–10g/day, equating to 14–20g LCT or 30–40g LCT from OO/LCT mix. IV FO administration: 0.1–0.2g/kg/day. FO containing LE have been shown to be anti-inflammatory and contain less hepatotoxic phytosterols

Abbreviations: ESPEN: European Society of Clinical Nutrition and Metabolism; CCPG: Canadian Clinical Practice Guidelines; ASPEN: American Society of Parenteral and Enteral Nutrition; EFAs: Essential Fatty Acids; ICU: Intensive Care Unit; IVLE: Intravenous Lipid Emulsion; LCT: Long-Chain Triglyceride; MCT: Medium-Chain Triglyceride; SO: Soybean oil; US: United States; FA: Fatty acids; OO: Olive oil; FO: Fish oil.

2.3.4.2 Lipid emulsions: Overview of clinical benefit

Lipid emulsions for PN provide a high amount of calories at a low osmotic load. They are composed of plant and/or fish oils containing FA. Their varying FA compositions partly account for their differential properties, both under physiological and pathophysiological conditions. Parenteral FAs interfere with immunological and inflammatory processes, thereby potentially influencing patient outcome. Inadequate or deregulated inflammatory and immune responses during acute stress can be responsible for increased complications such as nosocomial infections and organ failure. On the other hand, an appropriate and optimal PN may enable a better control of inflammatory processes and immune responses and thus improve critically ill patient outcome, defined by mortality, organ dysfunction and ICU or hospital LOS (1).

Adverse events should be carefully assessed with clinical and biological monitoring (TGs, inflammatory markers, liver and lung functions). Discrepancies occur between the different clinical and experimental study results partly owing to the lack of standardised criteria and because of the different PN formulations. Moreover, the clinical relevance of animal models has been largely criticised over the past years, as they invariably fail to reproduce the complexity of human illness (1). Human studies conducted in adult patient populations, comparing FOLE with other comparators, are discussed later in this review.

2.3.4.2.1 Critical illness

According to the ESPEN definition, a critically ill patient is a patient developing an intensive inflammatory response with failure of at least one organ (SOFA Score > 4), necessitating support of organ function during an ICU episode expected to be longer than three days (68).

Septic shock is a systemic inflammatory syndrome leading to profound mononuclear cell activation, which can evolve towards MOF and death. Hence, modulating excessive and deregulated inflammation by optimising artificial nutrition composition will be of major benefit (1).

The biological effects associated with LE are likely to benefit a majority of patients under metabolic stress receiving PN. The potential therapeutic benefits of LE are tabulated below (Table 2-15).

Table 2-15: Potential therapeutic effects of LE (1, 10, 124)

- Provide sufficient FAs
- Improve metabolism and limit energy deficit
- Maintain or increase antioxidant concentrations
- Limit the contribution of lipid peroxidation to oxidative stress
- Support the immune function and limit immunosuppression
- Reduce the incidence of infectious complications
- Prevent or regulate hyperinflammation

As far back as 1989 Griffin highlighted that reversing the negative nitrogen balance in septic patients would probably be impossible to achieve without therapeutic manipulation of cytokine or cyclooxygenase inhibitors (140).

Numerous studies in ICU patients indicate the clinical value of n-3 PUFAs in critically ill patients. (See Table 2-16) Mayer et al. (141, 142) showed that n-3 PUFA infusion for 5 days increased free n-3 PUFAs and reversed the n-6:n-3 PUFA ratio within 24 to 48 hours to an n-3 over n-6 predominance. Moreover, n-3 PUFAs 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) were decreased by 30% in patients treated with FO, whereas they were doubled in those treated with LCTs (n-6 PUFAs).

In a multicentre study in 661 critically ill patients, Heller et al. demonstrated that IV FO administered for ≥3 days improved survival and reduced infection rates, antibiotic requirements, and LOS at doses of 0.15 – 0.2g FO/kg/day (143).

A randomised study conducted by Khor et al., comparing IV FO vs saline in 28 critically ill patients with severe sepsis showed a significant score reduction for APACHE II and serum PCT on day 3, 5 and 7 in the FO group. However, serum TNF-α level, length of stay (LOS) of ICU and hospital stay were not significantly different in both groups (13).

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 MV, ICU LOS and mortality. The FO group tended to have a shorter hospital LOS which became significant when only surviving patients were included (144). 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 (145).

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 (146).

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) (147).

Another study conducted by Hall et al. in 60 critically ill patients with sepsis looked at the effects of parenteral n-3 PUFAs (0.2g FO/kg/day) administered as an independent drug additional to 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 (148).

Edmunds et al. compared the effects of different IVLEs on clinical outcomes in critically ill patients and showed that compared with lipid-free PN, patients who received FO had a faster time to ICU discharge alive. When compared with LCT, patients who received OO or FO had a shorter time to termination of MV alive and a shorter time to ICU discharge alive (149).

Four meta-analyses have looked at different LEs in critically ill patients (150-153). They found no difference in mortality but a significant reduction in hospital LOS with IV FO LE. However, two meta-analyses showed significant reduction in infection rate in the group receiving FO-supplemented PN (150, 152). In addition, Pradelli et al. showed reduced markers of inflammation in the FO group, especially IL-6 and a shift towards LTB_5 series production (152). He conducted a cost-effectiveness analysis on PN regimens containing omega-3 PUFAs in ICU patients. The reduction in infection rates and overall LOS translated to a cost saving of between €3972 and €4897 per ICU patient (154).

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 with other IVLEs (155).

Table 2-16: Clinical studies in septic patients

Study	Patients	Duration	Lipid Emulsion	Effects
Barbosa (144)	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 (145)	20 sepsis & 20 SIRS pts	7 Days	MCT/LCT + FO vs MCT/LCT (FO 0.6g/kg)	**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. Serum LDH & TG significantly ↑ on D7 & D10 for SIRS grp 7 only ↑ on D7 in sepsis grp. **FO grp**: IL-10 significantly ↑ on D3 & D7 in sepsis grp.
Friesecke (147)	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 (148)	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 (149)	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.

Study	Patients	Duration	Lipid Emulsion	Effects
Khor (13)	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 (141)	21 septic pts	5 days	LCT vs LCT + FO (35g/day)	**FO grp**: ↓ cytokine secretion. ↑ EPA & DHA after Day 3. n-6:n-3 PUFA ratio=2.5:1 after day 3. No effect on length of MV & mortality.
Mayer (142)	10 septic pts	10 days	LCT vs LCT + FO	**FO grp**: ↑ EPA & DHA over AA. ↑ LTB_5. Improved neutrophil function. ↓ CRP on D4. Improved n-6:n-3 PUFA ratio. No effect on length of MV & mortality.
Heller (143)	661 ICU pts	≥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 (146)	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 (156)	159 ICU pts	≥ 5 days	MCT/LCT vs LCT/MCT/FO (FO 0.1g/kg)	FO grp: Fewer instances of nosocomial infections (21% vs 37.2%). Similar clinical outcomes (mortality, hospital LOS, ICU stay, days 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 aminotransferase; GGT: gamma-glutamyl transferase; IL-6: Interleukin-6; IL-1β: Interleukin-1β; TNF-α: tumour-necrosis factor-alpha; LDH: lactate dehydrogenase; PaO_2/FiO_2: partial pressure arterial oxygen and fraction of inspired oxygen ratio; n-6:n-3 PUFA: omega-6:omega-3 polyunsaturated fatty acid ratio.

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2.3.4.2.2 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. Moreover, 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 imaging studies demonstrating diffuse pulmonary infiltrates (157). The PaO_2/FiO_2 ratio in mild ARDS is 200mmHg– ≤300mmHg, in moderate ARDS is 100mmHg–≤200mmHg and in severe ARDS is ≤100mmHg (158). The role of nutrition in the management of ARDS has traditionally been supportive. Recent research has 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 mechanical ventilation (157).

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 (159, 160). The deleterious effects appear to be predominantly due to their high proportion of LA and to excessive or rapid LCT infusion (161). This results in a reduction in PaO_2/FiO_2 ratio, pulmonary blood pressure and vascular resistances, through an imbalance in production of vasodilating and vasoconstricting eicosanoids (160, 162).

Emulsions with mixtures of FA have been administered to reduce the deleterious effects of high doses of omega-6 FA, while replacing the carbohydrate energy source by lipids. In addition the omega-6:omega-3 ratio is significantly reduced in the latest generation LE (1). Morlion et al. suggested that in patients receiving PN, a n-6:n-3 PUFA ratio of approximately 2:1 may be optimal (134).

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 and there were fewer patients with PaO_2/FiO_2 <200 and <300 in the fish-oil group; however, days on MV were not different between the two groups (144). Another study (163) using the same LEs 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 didn't show significant changes in haemodynamic and gas exchange parameters (164).

Similar results have been shown in studies using n-3 PUFAs as part of enteral nutrition (165-168); however this will not be discussed as this falls beyond the scope of this review.

2.3.4.2.3 Lipid emulsions and surgical patients

There are numerous clinical studies (Table 2-17) on the efficacy and safety of LE in surgical patients. LCTs were the first LEs used in post-surgical patients and were found to increase pro-inflammatory cytokines and decrease T-cell proliferation in stressed patients, while having no effect in unstressed patients (169).

There is data using fish oil containing LE in surgical patients showing a good safety profile, generation of n-3 fatty acid-derived lipid mediators and a reduced length of stay. The use of fish oils in this group of patients has shown improved plasma levels of α-tocopherol and better liver tolerance (170-177). Based on a review of the available evidence, Mayer concluded that inclusion of n-3 PUFAs in PN improves immunologic parameters and LOS in surgical patients (178).

A meta-analysis conducted by Chen et al. (179) looked at 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 were also reduced and plasma α-tocopherol increased. These results were also confirmed in the meta-analysis by Wei et al. (180). Tian et al. showed similar results in terms of reduction in liver enzymes, triglycerides and CRP in the FO group; however, showed no difference in hospital LOS (181).

Recently, a more extensive meta-analysis was performed to analyse the clinical efficacy and safety of n-3 PUFA-enriched parenteral LE in elective surgical and ICU patients. The results showed that n-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 (152). See Table 2-18 for meta-analyses on FO containing PN.

Table 2-17: Clinical studies in post-surgery patients

Study	Patients	Duration	Lipid Emulsion	Effects
Antebi (170)	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 (174)	199 post-op 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 (182)	44 post-op patients	5 days	LCT/MCT/OO/FO vs OO/LCT	**LCT/MCT/OO/FO grp** : improved liver function.
Berger (183)	20 patients with AAA surgery	4 days	LCT/MCT/FO vs MCT/LCT	**LCT/MCT/FO grp:** no significant difference in laboratory parameters & clinical outcome. Significant↑ EPA & DHA on Day 4. No difference in TG levels. Trend for shorter ICU and hospital stay.
Han (172)	30 post-op major surgical 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. ↓ in infection rate and liver dysfunction. No difference in mortality.
Wu (184)	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. FO grp: non-significant trend for shorter hospital stay.
Tsekos (185)	249 ICU pts Major abdominal surgery	2-year 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.

Study	Patients	Duration	Lipid Emulsion	Effects
Zhu (186)	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 (187)	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 (176)	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 (173)	206 GI cancer surgical pateints	7 days	LCT vs LCT/FO	**FO grp**: Less infectious complications & significantly ↓ SIRS. Hospital LOS significantly ↓
Wei (188)	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 (189)	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 (171)	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 . ↑LTB_5:LTB_4 ratio. ↑LTB_5 release and ↓ LTB_4

Study	Patients	Duration	Lipid Emulsion	Effects
Heller (190)	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 (191)	661 post-op & septic pts	≥ 3 days	Different n-6:n-3 PUFA ratio	n-6:n-3 ratio 2:1 ↓ ICU LOS. No difference in mortality.
Genton (192)	32 post-op patients	7–14 days	LCT vs LCT/MCT/OO/FO	No difference in TG, total cholesterol and liver functions.
Ma (193)	99 gastrointestinal cancer surgery patients	1 day before & 7 days post-op	MCT/LCT/FO vs MCT/LCT	**FO grp**: Improved lipid metabolism. No effect on metabolic parameters, pro-inflammatory cytokine levels, adverse events and clinical outcomes.
Metry (194)	83 postoperative ICU patients	7 days	LCT/MCT/OO/FO vs LCT	No significant differences with regard to vital signs and laboratory profiles of cholesterol, TG and liver enzymes. IL-6 levels were significantly different between 2 group on D4 & D7; IL-6 was significantly lower in FO group on D4 & D7.
Senkal (195)	40 colorectal surgery patients	5 days	MCT/LCT vs LCT/MCT/FO	**FO grp**: significant ↑ in EPA and DHA levels. Increase in n-6:n-3 PUFA ratio. AA not significantly different in both groups
Wichmann (177)	256 major abdominal surgical patients	5 days	LCT vs LCT/MCT/FO	**FO grp:** ↑in EPA, LTB_5 and α-tocopherol levels. ↓n-6:n-3 ratio on d6. Shorter length of hospital stay (17.2 days versus 21.9 days). No difference in mortality.

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; D: days; AA: arachidonic acid; EPA: eicosapentanoic acid; DHA: docosahexaenoic acid

Table 2-18: Meta-analysis on FO-containing PN

Author	Patients	No. of Studies	Lipid Emulsion	Effects
Pradelli (152)	1502 surgical & ICU patients	23	FO-enriched PN vs LCT, MCT/LCT or OO/LCT	**FO grp**: Significant ↓ in infection rate, LOS in ICU & hospital. Reduced markers of inflammation, especially significant reduction in IL-6, shift towards LTB_5 series, improved lung gas exchange, significant ↓ in ALT & AST, ↑ in antioxidant status & FA composition of plasma phospholipids. No difference between coagulation times, platelet count, serum TG, CRP or bilirubin. No difference in mortality.
Tian (181)	306 surgical pts	6	LCT/MCT/OO/FO vs LCT, MCT/LCT or OO/LCT	**FO grp**: Lower levels of liver enzymes, significant difference in AST between FO & LCT grp. ↓ in TG & CRP vs LCT & OO/LCT grp. No difference in hospital LOS. No difference between MCT/LCT vs LCT/MCT/OO/FO.
Chen (179)	892 major abdominal surgical pts	13	FO PN vs PN + other LE	**FO grp:** ↓ hospital & ICU LOS, post op infection rate, levels of AST & ALT, ↑ α-tocopherol on POD6. Significant differences in EPA & DHA levels but not AA. LTB_5:LTB_4 ratio significantly enhanced in FO grp. No difference in mortality, cardiac complications or bilirubin & TG levels.
Palmer (151)	391 critically ill pts	8	FO-supplemented PN	Significant reduction in hospital LOS. No difference in mortality, infectious complications & ICU LOS.
Manzanares (150)	733 critically ill pts	10	FO LE vs EN, PN with SO-based LEs or a non-FO based LE, including saline solution	FO significantly ↓ infections & hospital LOS. No effect on overall mortality.
Wei (180)	611 surgical pts	6	FO LE vs MCT/LCT or LCT or OO	**FO grp**: Significant ↓ in infectious complications. Trend to shorter hospital LOS. Significant ↓ in ICU LOS. No mortality benefit.

Author	Patients	No. of Studies	Lipid Emulsion	Effects
Kreymann (196)	380 critically ill pts 1005 surgical pts with malignancies		FO LE + OO/SO FO LE + MCT/LCT LCT/MCT/OO/FO LCT/MCT/FO	35% reduction in infection rates in critically ill pts and 59% reduction in surgical pts with malignancy. Significant reduction in IL-6 levels. Significant reduction in hospital LOS by 1.84 days in surgical pts.

Abbreviations: Pts: patients; LOS: length of stay; ICU: intensive care unit; FO: fish oil; LE: lipid emulsion; IL-6: interleukin-6; LTB_5: leukotriene B_5; ALT: alanine aminotransferase; AST: aspartate aminotransferase; FA: fatty acid; EN: enteral nutrition; PN: parenteral nutrition; CRP: C-reactive protein; TG: triglycerides; LCT: long-chain triglyceride; MCT: medium-chain triglyceride; OO: olive oil; POD6: post-operative day 6; LTB_4: leukotriene B_4

2.3.4.2.4 Lipid emulsions and 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. In studies conducted in Spanish ICUs, the prevalence of such changes has been reported in 30% of critically ill patients on PN. If liver involvement progresses, it may lead to cirrhosis, and liver and bowel transplant may be required (83).

Diagnosis is mainly based on bilirubin and liver enzyme levels and the cut-off values change depending on the hospital or in different studies. Moreover, the correlation between changes in laboratory tests and histopathological findings in liver biopsies is low. The etiology of changes is thought to be multifactorial (see Table 2-19) (197).

Table 2-19: Factors associated with liver changes associated with PN (10, 11, 83, 197)

Changes associates with PN:

- Duration on PN
- Overfeeding, particularly with calories
- CHO overload
- Lipid overload and high phytosterol intake
- Amino acid overload or deficiency
- Carnitine, choline or taurine deficiency
- Excess manganese and copper administration
- Long-term continuous infusion

Patient-associated factors:

- Underlying disease
- Sepsis
- Intestinal bacterial overgrowth
- The presence of short-bowel syndrome
- Lack of enteral nutrition
- Hyperinsulinism

There are four factors with regard to lipids in PN that have been related to liver dysfunction.

a. Lipid dose

Both a deficiency and an excess provision of essential FA may cause liver damage. A lipid dose of > 1g/kg/day is associated with a marked increase in liver changes and a 2 – 5 times greater risk of experiencing some severe change in the liver (198). At least 2–4% of total calories should be administered as linoleic acid to prevent deficiency. The ratio of calories provided by CHOs and

lipids also appears to be important and should not exceed 60:40 in home patients (199). The mechanism by which toxicity is related to the lipid dose is not clear, but it could be changes in liver macrophages, phospholipid elimination in bile, or a blockade of liver capacity to mobilise lipids (127, 197, 198).

b. Lipid composition

LE based on SO, with high n-6 PUFA content, have been associated with greater liver toxicity, particularly when they are used over a long period of time (10,11). To decrease this toxicity, an alternative LE with lower n-6 FA content (e.g. MCTs) as well as n-3 PUFAs have been proposed (170, 182).

c. Phytosterols

LEs are mostly of plant origin and contain substantial amounts of phytosterols. See Table 2-12 for the phytosterol content of IVLE. These phytosterols have been related to liver toxicity in PN because they are considered to be able to alter cholesterol and bile acid production and to contribute to cholestasis (11, 136).

d. α-Tocopherol

This may act as a potent antioxidant in cases of steatosis, protecting the liver from oxidative damage. Omega-3 PUFA LEs have greater amounts of α-tocopherol than those derived from SO (200). See Table 2-12 for α-tocopherol content in IVLE.

The effects of FO-containing LEs compared with other LEs on liver dysfunction have been studied in surgical patients. FO LEs showed improvement in liver enzymes and plasma α-tocopherol levels (170, 171, 174, 176, 182, 186, 189). Some studies showed no difference in terms of liver function tests with FO LEs (184, 188, 192).

Sungurtekin et al. demonstrated an increase in liver steatosis on day 7 and 10 in patients with sepsis and SIRS on PN without FO (145). 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 (0.71g FO/kg – 5.28g FO/kg) (201).

Two studies were conducted in patients undergoing liver transplantation, comparing PN with and without FO. A significant reduction in ALT and prothrombin time was seen in the FO group and a significant decrease in post-transplant hospital stay (202, 203).

Reduction in liver enzymes and improved antioxidant status was also shown in four meta-analyses (152, 179, 181, 204) . The dosage of FO that showed benefit was 0.1 – 0.15g/kg/day (152) and 0.07 – 0.225g/kg/day (179).

Klek et al. (205) performed a study to evaluate the safety and efficacy of a soybean/MCT/olive/fish oil containing 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.

2.3.4.3 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 (125). The tolerance of lipids is monitored by measuring plasma triglyceride 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 the administration of steroids are two examples of factors which decrease LPL activity (206).

LCT and LCT/MCT LEs have been shown to increase plasma triglyceride levels, whereas FO containing LEs have been shown to reduce plasma triglyceride levels significantly in both surgical and septic patients or maintain the levels within normal ranges (170, 172, 174, 182-184). (Tables 2-15 & 2-16.)

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 with PN without FO (179). However, the meta-analysis conducted by Tian et al. found significant differences between LCT/MCT/OO/FO vs LCT and vs OO/LCT, suggesting the beneficial effect of FO containing LE in surgical patients (181).

In general, IVLE should not be infused in patients with plasma triglycerides (TGs) >3–4 mmol/l and should be closely monitored in those with high basal (>2–3mmol/l) TG concentrations to avoid complications (11). 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 (65).

b. Fat overload syndrome

Fat overload syndrome is another complication of IVLE therapy. It is characterised by headaches, jaundice, hepatosplenomegaly, respiratory distress and spontaneous haemorrhage. It has been described in several case reports in the presence of rapid infusion and/or high doses of IVLE. Other symptoms of fat overload include anaemia, leukopaenia, thrombocytopaenia, 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 (125). Guidelines from ESPEN recommend that IVLEs be administered at a rate of 0.7 – 1.5 g/kg over 12 – 24 hours (11). FO LEs seem to reduce the risk of lipid overload by accelerating TG clearance more than SO LEs. Despite being cleared more efficiently, FO LEs undergo less catabolism than SO LEs. 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 TGs but rather enhances the clearance of emulsion particles and may not predispose patients to the complications associated with rapid infusion of SO LE (125).

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 & AST >40 IU/L) (83) and hyperbilirubinaemia (>34 µmol/L) (136). Risk factors for the development of parenteral nutrition-associated liver disease (PNALD) have been addressed previously. Refer to Table 2-19.

d. Essential fatty acid deficiency (EFAD)

Linoleic acid and alpha linolenic acid are the two essential FAs that cannot be synthesised by the human body. The typical ICU patient requires 9–12g/day LA and 1–3g/day ALA. Their importance is emphasised by their further metabolism to AA, EPA and DHA (68). Low essential FA intake eventually leads to EFAD, which is associated with water losses from the skin owing to increased permeability, susceptibility to infections, lowered resistance to irradiation injury and impaired wound healing, haematologic 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 (11). At least 2–4% of total calories should be administered as linoleic acid to prevent EFA deficiency (200) or essential FA should be provided at 7–10g/day, equating to 14–20g LCT or 30–40g/day LCT from OO/LCT mix (65).

e. Pulmonary complications

Parenteral SO LEs have been shown to induce inflammation of pulmonary vessels, leading to pulmonary hypertension, phagocyte activation, and the formation of granulomas (159, 160). 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 (11, 162).

The administration of FO LE has been shown to improve gas exchange and reduce pro-inflammatory eicosanoids (144 152).

f. Oxidative stress

Unsaturated FAs, such as LAs 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 (127).

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 (11).

g. Coagulation complications

Thrombosis is a common and serious complication for many critically ill, surgical and trauma patients. The patients might experience changes in the availability of clotting factors and alterations in the fibrinolytic pathway, resulting in disseminated intravascular coagulation (207). The effect of LEs on coagulation have not been extensively assessed (124).

Currently there is no evidence of adverse effects of FO LEs based on an increased bleeding risk due to their antiplatelet effects (152). Heller et al. (190), 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 0.2g/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 (205).

h. Immune function and infections

LEs can influence the immune system, as addressed previously; there are concerns that pure SO LEs might impair clinical outcomes due to their potential to promote inflammation and inhibit immune responses, especially in situations with an overproduction of pro-inflammatory mediators such as trauma or sepsis (see Table 2-16, 2-17 and 2-18). 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 (11).

It has been recommended that new lipid emulsions should be composed of a reduced n-6 PUFAs, especially linoleic acid, counterbalanced by MCT, MUFA and long-chain n-3 PUFAs. Based on experimental and clinical studies, the most favourable n-6:n-3 PUFA ratio is proposed to range between 2:1 and 4:1 (11, 133-135).

2.3.5 Micronutrients

Micronutrients play a central role in metabolism and in the maintenance of tissue function. Trace elements are involved in the activity of virtually all enzymes, whether at the active site of the enzyme or as co-factors. Vitamins act as co-factors. These are clearly necessary for the

maintenance of intermediary metabolism and adequate amounts are vital to the body's ability to cope with the metabolic response to critical illness. Hypermetabolism gives rise to increased production of ROS, as a result of increased oxidative metabolism. This may lead to oxidative damage at various points within the cell, but particularly to PUFAs in the cell membrane, or to nucleic acids in the nucleus. The body has a well-developed antioxidant system to neutralise the most harmful effects of these oxidant species. Micronutrients have important functions in this, either directly in the immediate quenching of the oxidative particle, for example the antioxidant action of vitamin E or C, or more indirectly as part of metallo enzymes such as glutathione peroxidase (selenium) or superoxide dismutase (zinc, copper) which catalyse removal of the oxidant species. The micronutrients also have other key functions, such as modulating gene transcription where they may be involved in either activation of particular genes, or in the control of this activation (208).

Recent findings suggest that Vitamin D is a marker for outcomes in critical illness. Vitamin D deficiency is defined as 25 (OH)-D concentrations < 50nmol/L and is common in hospitalised patients requiring long-term EN or PN (209, 210). The prevalence of vitamin D deficiency is considerably higher in patients with various disorders of the digestive system, including cystic fibrosis, acute and chronic pancreatitis, coeliac disease, short-bowel syndrome and inflammatory bowel disease (209). Restoration of optimal vitamin D status with high-dose supplemental vitamin D is required in most cases (210). A meta-analysis by De Haan et al. suggested that vitamin D deficiency increases susceptibility to severe infections and mortality of the critically ill (211); however no difference in 90-day mortality was reported by the FINNAKI cohort study (212). In severe vitamin D deficiency (<30nmol/L), lower mortality was observed with supplementation (58).

Adequate micronutrient (electrolytes, trace elements and vitamins) intake is essential to avoid depletion especially if refeeding syndrome is suspected (50). Guidelines on Parenteral Nutrition in ICU recommend that all PN prescriptions should include a daily dose of multivitamins and of trace elements (65, 68). ASPEN suggests that a combination of antioxidant vitamins and trace minerals in doses reported to be safe in critically ill patients be provided to those patients who require specialised NT (66). However, most issues of administration, such as dosage, frequency, duration and route of therapy, have not been well standardised as there is not good evidence to inform this. See Table 2-20: Parenteral recommendations of micronutrient intake in critical illness.

Table 2-20: Parenteral recommendations of micronutrient intake in critical illness (65, 213-216)

Micronutrient	Recommended intake	Amount provided in PN per day
Thiamine	1.1–300mg	2.5mg
Riboflavin	1.1–3.6mg	3.6mg
Niacin	35–40mg	40mg
Folic acid	400–1000µg	400µg
Pantothenic acid	5–15mg	15mg
Vitamin B6	1.3–6mg	4mg
Vitamin B12	2.4–5µg	5µg
Biotin	30–60µg	60µg
Ascorbic acid	100mg–2000mg	100mg
Vitamin A	700–3000µg	1980µg or 3300IU
Vitamin D	5–50µg	5µg or 200IU
Vitamin E	10–1000mg	9mg or 10IU
Vitamin K	90–1000µg	150µg

Adapted from ASPEN 2002, Sriram 2009, Berger & Shenkin 2006, Visser 2014, & SA National DoH Guidelines on PN 2016.

2.4 Monitoring

Close monitoring on all patients receiving PN daily should include assessment of clinical, laboratory and nutritional indices (see Table 2-21 and 2-22). This guarantees that the nutrition prescription is appropriate and adequate and that the risks of complications are minimised (63, 70).

Table 2-21: Clinical evaluation on PN patients (63, 65, 70, 213)**.**

Parameter	**Evaluation**	**Frequency**
Vital signs	Temperature, blood pressure, respiratory & heart rate	Hourly in unstable patients, 6-hourly in stable patients
Physical examination	Abdomen: • distention or discomfort • Stool/ostomy/fistula output & consistency Fluid balance	Daily Hourly in unstable patients otherwise daily
PN bag	Leaking, cracking or separation of content	Ongoing
Infusion rate & pump	Correct rate & pump is running	Ongoing
Line site	Infection, inflammation, oedema, rash & tenderness	Daily
General response to therapy	Wound healing, functional status, muscle & protein stores & micronutrient status	Ongoing
Nutritional intake	Adequacy of delivery, readiness to introduce enteral or oral nutrition	Daily

Table 2-22: Biochemical monitoring during PN administration (63, 65, 70)

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 normalised ratio; Vit: vitamin

Serum phosphate, magnesium, potassium, and glucose should be tested if the patient is at risk of refeeding syndrome and replaced if depleted, before starting NT. Further close monitoring of these electrolytes is imperative (51, 213).

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. (63, 70).

2.5 Conclusion

Sepsis remains the leading cause of death in critically ill patients. These patients have life-threatening organ dysfunction caused by a dysregulated host response to infection(16). The metabolic response to stress is complex and many patients experience ongoing immune dysregulation and develop persistent inflammation, immunosuppression and catabolism syndrome (3).

Critically ill patients depend on artificial nutrition for the maintenance of their metabolic functions and lean body mass (63). Parenteral nutrition is a well-tolerated and important mode of nutrition for ICU patients, if correctly prescribed. Recent evidence points to the importance of early and adequate feeding in critically ill patients. However, special attention is needed to avoid overfeeding during the first 2–3 days in the ICU (79). Many of the deleterious effects attributed to PN result from wrong indications, composition of the formulation and/or from overfeeding (63).

Lipids are undoubtedly an indispensable element of PN regimens, as they are not only an important energy source, they provide essential FA and can also modulate metabolic processes (10). The composition of LE has evolved over the years and the development of improved formulations are characterised by four distinct generations (125).

The addition of FO to nutritional regimens in critically ill patients offers the possibility to counterbalance the unfavourable effects of SO LEs and n-6 PUFAs on immune system function and regulation of vascular tone. There is data on the use of n-3 lipids in surgical and ARDS patients; however the results are variable. In addition, there is some initial promising data on their use in septic patients (124, 125, 178). The results of the various studies are variable owing to study heterogeneity, varying quality and study design, small sample sizes, and differences in the timing and dose of FO administration as well as the different LEs studied (155).

To date there is no study comparing the use of a combination 4-oil lipid emulsion containing fish oil (SMOFlipid®) in septic patients. In South Africa this LE is readily used in ICUs in critically ill patients and it would thus be beneficial to have data showing efficacy and safety, as well as improved oxygenation, reduced inflammation, improved total phospholipid plasma FA composition, and improved clinical outcome in this group of patients.

It was hypothesised that including FO as part of a 4-oil LE in patients with SIRS, with or without sepsis, or ARDS, requiring PN may be associated with less inflammation, improved gas exchange, increased plasma EPA, modified plasma total phospholipid fatty acid profile and improved clinical outcomes.

The research questions are:

What is the effect of a 4-oil LE-containing FO as part of PN in terms of effect on triglyceride levels and liver enzymes?

Does the inclusion of a 4-oil LE-containing FO in PN result in less inflammation, by reducing the pro-inflammatory cytokines TNF-α, IL-1β and IL-6, and maintaining the levels of anti-inflammatory cytokine, IL-10?

Does the inclusion of a 4-oil LE containing FO in PN result in improved gas exchange?

Does the inclusion of a 4-oil LE containing FO in PN increase plasma EPA and modify other plasma total fatty acids?

Will the inclusion of a 4-oil LE containing FO in PN improve clinical outcomes?

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CHAPTER 3

METHODOLOGY

3.1 Aim

To compare the difference between a 4-oil lipid emulsion containing fish oil (SMOFlipid®) and a 100% soybean-based lipid emulsion in patients with the Systemic Inflammatory Response Syndrome (SIRS) with or without sepsis, or the acute respiratory distress syndrome (ARDS) in the intensive care unit (ICU), requiring parenteral nutrition (PN) for more than 5 days.

3.2 Objectives

To compare a 4-oil lipid emulsion (SMOFlipid®) containing omega-3 fatty acids from fish oils to a soybean-based lipid emulsion rich in omega-6 fatty acids, in terms of it's impact on

1. the inflammatory response; c-reative protein, tumour necrosis factor alpha (TNF-α), Interleukin-1β (IL-1β), IL-6 and IL-10,
2. gas exchange, measuring PaO_2/FiO_2 ratio in patients with SIRS, or sepsis or ARDS,
3. plasma EPA levels, and
4. clinical outcome in terms of Sequential organ failure assessment (SOFA) score, length of ICU stay and mortality.

3.3 Implementation objectives

The results from this study will assist prescribers of PN to optimised nutrition therapy for critically ill patients with sepsis, in particular with regards to the type of lipid emulsions used in the PN prescriptions.

3.4 Study design

Double-blind, randomised, multi-centre, controlled trial.

3.5 Study population and sampling

3.5.1 Study population

The study population consisted of adult (i.e ≥ 18 years) patients with SIRS with or without sepsis or ARDS in ICU, which were recruited from the multi-disciplinary ICU and surgical ICU at Universitas,

ICU at Pelonomi Hospital in Bloemfontein, and ICU and high care at Wits Donald Gordon Medical Centre (WDGMC).

At Universitas Hospital the multi-disciplinary ICU had 7 beds and the surgical ICU had 4 beds. Pelonomi Hospital had 10 ICU beds. The ICU at WDGMC had 15 beds and High Care had 16 beds. (Appendix A: Data collection Protocol)

The study was initially planned to be a multicentre study, however the recruitment at Universitas and Pelonomi hospital was very slow owing to challenges in the healthcare administration in the province and subsequently only 9 patients were recruited in 10 months. It was decided to open another centre at Wits Donald Gordon Medical Centre (WDGMC), Johannesburg, to continue with the study and to close the centres in Bloemfontein. Only the patients recruited from WDGMC were included in the two manuscripts. It was decided to exclude the patient recruited in Bloemfontein as there were insufficient biochemical results (namely cytokine and plasma fatty acid analysis).

3.5.2 Sample size

The total number of study participants needed was determined, with the help of a statistician, to be at least 72 individuals (36 in each subgroup). This number was calculated using a power analysis for ANOVA with two groups, significance level of 0.05 and an effect size of 0.55. Sample size n=36 in each group was expected to yield 90% power to detect this effect size (Appendix C).

A total number of 84 patients were included into the study, however 16 patients were excluded due to insufficient biochemical results (10 patients), protocol violations (4 patients) and 2 patients withdrew consent, leaving a total of 68 patients. Thirty five patients were randomised to the study group (SG) and 33 patients to the control group (CG).

3.5.3 Sampling

All patients admitted to the ICU or high care units were screened for eligibility. A screening form was completed with columns representing the eligibility criteria of each patient to be included.

Consecutive patients meeting the inclusion criteria were enrolled in the study until the required sample size was reached. Data collection commenced in the last week of June 2014 in Bloemfontein at Universitas and Pelonomi Hospital and in April 2015 at WDGMC. Data collection was completed on 9th June 2016. (Appendix A: Data collection Protocol)

Adult patients (>18 yrs) male or female with SIRS with or without sepsis or ARDS admitted to the ICU, who were predicted to need PN for more than 5 days were entered into the study.

3.5.4 Inclusion and exclusion criteria

3.5.4.1 Inclusion criteria

The inclusion criteria for this study was as follows;

- all adult patients (>18 yrs) male or female admitted to ICU
- with SIRS with or without sepsis,
- or ARDS, and
- predicted to need PN for more than 5 days.

3.5.4.2 Exclusion criteria

The exclusion criteria for this study included patients

- Younger than 18 years,
- on full enteral feeding,
- pregnancy,
- treatment with immunosuppressive drugs,
- treatment with hydrocortisone >300mg/day at admission,
- plasma triglycerides >400mg/dl (4,52mmol/l)
- chronic liver disease and/or acute hepatitis,
- chronic renal failure and/or end stage renal disease (According to the Rifle criteria, Appendix AI Table 3),
- recent stroke,
- known allergic reaction to fish or egg proteins confirmed by previous medical history.

3.6 Methods of data collection

Once the screening form (Appendix AII) was completed and the eligibility of the patient assessed, the patient was requested to complete the consent form (see Appendix B). If the patient was unable to give consent, the closest relative was asked. If the closest relatives are unable to give consent, the Clinical Manager at the site decided if the patient could be included into the study.

The patient was re-consented when it was possible. Once consent was obtained, the patient was allocated a research number and the research assistant started the data collection.

3.6.1 General data collection procedure

The clinician in charge of the study participant decided when the PN should commence, the dietitian was consulted to do a nutritional assessment on the patient and recommended a PN prescription to the clinician. The clinician ordered blood tests according to the laboratory measurements protocol before PN was started. The PN prescription form, was completed by the dietitian and signed by the clinician. The hospital pharmacy was contacted to inform them of the PN prescription and the patient's inclusion into the study. The hospital pharmacy then contacted Fresenius Kabi Bloemfontein or Johannesburg (the supplier of PN), and placed the order for PN and explained that the patient was participating in the study.

On receiving the PN prescription, the dispensing pharmacists in Bloemfontein or Johannesburg were responsible for the randomisation of all the patients according to a randomisation sheet. This sheet allocated the type of PN according to the ITN code to the patient's research number, name, file number, ICU and hospital.

The patients was randomised to either receive PN containing a 4-oil lipid emulsion (SMOFlipid®: 30% LCT, 30% MCT, 25% Olive Oil, 15% Fish oil, provided in a complete All-in-One PN bag by Fresenius Kabi: study group) or a Soybean-based lipid emulsion (Intralipid® 100% LCT, provided in a complete All-in-One PN bag by Fresenius Kabi: control group).

The all-in-one PN, was compounded using isolator technology according to a validated procedure at Fresenius Kabi in Midrand, Johannesburg. The compounded PN bags all looked identical and were only differentiated by a barcode. The PN bags were stored at 2^0C - 8^0C in Johannesburg and then flown to Bloemfontein in a controlled temperature environment. On arrival in Bloemfontein the PN bags were refrigerated until they were dispensed to the various hospitals participating in the study.

Before the PN was dispensed, a special sticker was placed on the outer pouch as well as the PN bag to identify it as a study bag and to avoid confusion when all the PN was delivered to the hospitals participating in the study. The outer pouch and PN bags look exactly the same, a label with the patient's name, hospital, ward information and the nutritional composition of the bag was placed on the outer pouch and on the PN bag. This guaranteed that the correct PN was administered to the correct patient.

The dispensing pharmacist checked that the correct bag was dispensed to the correct patient according to the randomisation sheet.

The PN bags were delivered to the hospital pharmacy before 14h00 daily. On receiving the PN, the hospital pharmacy dispensed it to the ICU where the appropriate patient was. The PN bags were refrigerated until the nursing sister was ready to administer the PN. The PN was administered continuously over a 24 hour period. The PN was started on the day after admission to the study (day 2).

Fresenius Kabi Bloemfontein and Johannesburg employ a dispensing pharmacist and as well as a locum pharmacist. These two people are the only ones who had access to the randomisation sheet and were involved in the dispensing of the PN. The randomisation sheets were kept locked away in a cabinet for safe keeping. Only the pharmacist and locum pharmacist had access to the keys of the cabinet and the randomisation sheets. Once the study was completed, the randomisation sheets were obtained from the pharmacist and the study was un-blinded.

The research assistant entered all the patient information required on the case report form daily until the patient was discharged (see Appendix AIII).

By following the above procedure there was no deviation from usual standardised PN prescription techniques. The only difference being the fat composition of the PN bags. All the patient information was recorded daily until discharge from the ICU.

3.6.2 Sociodemographic and general medical data

The patient's admission date, gender, age, primary diagnosis, SOFA score, APACHE II score was documented on entry into the study. The RIFLE classification to determine renal failure and the SOFA score was documented throughout the study.

3.6.3 Baseline anthropometrical data

3.6.3.1 Height

The dietitian or research assistant measured the study participant's height with the patient lying flat in bed, or used the height charted on the ICU chart

3.6.3.2 Body Weight (BW)

Weight charted on the study participant's ICU chart was used. If there was no admission weight recorded, the dietitian estimated the patient's weight. The patient's Body Mass Index (BMI) was calculated on admission using estimated weight (kg)/height in m^2 and recorded. The patient was then classified as undernourished, normal, overweight or obese according to the table in the case

report form (Appendix AIII). The dietitian documented which weight was used for calculations and any adjustments made to the weight, e.g. for underweight or overweight. All the above baseline measurements were recorded by the research assistant (see Appendix AIII and AIV).

3.6.4 Nutritional prescription

The study participant's energy and protein requirements were calculated individually using the American Society of Parenteral and Enteral Nutrition (ASPEN) and European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines (25 – 30kcal/kg/day total energy (TE) and protein 1.2g – 2g/kg/day) (see Appendix AIV; SOP for calculating nutritional requirements). Both groups of study participants received glutamine, vitamins, minerals, trace elements and electrolytes as part of the complete PN. The PN prescription form (see Appendix AV) was completed by the dietitian and signed by the clinician. The PN order was then placed at the hospital pharmacy. The hospital pharmacy then contacted Fresenius Kabi Bloemfontein or Johannesburg with the PN orders for the day.

The PN bag, in SG or CG, were prescribed according to the study participant's requirements and the administration rate was adjusted accordingly. (see Table 3-1 for the composition of the PN bags). The dietitian clearly marked the PN administration rate on the study participant's ICU Chart.

Table 3-1: The composition of the Parenteral Nutrition Bag is as follows:

Contents of PN	ITN 8807	ITN 8007
Fluid	2390ml	2390ml
Total Energy	2220	2220
Energy (NPE)	1800kcal	1800kcal
Carbohydrates	200g (45% of NPE)	200g (45% of NPE)
Fat Soybean oil MCT Olive oil Fish oil: EPA + DHA n-6:n-3 fatty acid ratio	100g (55% of NPE) 30g 30g 25g 15g 4.6g 2.5:1	100g (55% of NPE) 100g 0 0 0 0 7:1
Nitrogen	16.8g	16.8g
Glutamine	15g	15g
Vitamins, minerals and trace elements	RDA	RDA
Osmolarity	981mOsm/l	978mOsm/l
Abbreviations : NPE: Non-Protein Energy ; RDA: Recommended Daily Allowance ; MCT : Medium Chain Trigylcerides ; EPA : Eicosapentaenoic acid ; DHA : Docosahexaenoic acid		

The nursing staff looking after the patient removed the PN bag from the fridge 1 hour before it was administered to the study participant. Aseptic techniques were used according to the hospital protocol to administer the PN bag. The nursing staff checked that the PN bag was correct for the study participant and as well as the rate at which the PN bag needed to be administered. Once the PN bag was connected to the study participant, the nursing staff documented the time at which the PN bag was started and the rate. The study participant was monitored according to the ICU protocol. All information was recorded on the study participant's chart. The research assistant recorded all the relevant nutritional prescription and administration on the case report form.

3.6.5 Daily fluid and nutritional data

Fluid input and output data was collected daily, according to the case report form as well as nutritional prescription versus nutrition delivered. (see Appendix AIII). Other intravenous fluids administered were documented and their composition was assessed to determine the effect on the study participant's energy intake. Medication was also documented, particularly medication that could contribute to the study participant's fat and energy intake, e.g. Propofol® and glucose-containing IV fluids. The SOFA score (Appendix AI table 2) was assessed on a daily basis. The patient's renal function was also assessed daily using the RIFLE classification (Appendix AI table 3).

3.6.6 Biochemical data

a. Routine blood samples:

All blood samples were collected on admission, immediately prior to starting the PN (day 1), 24hr after initiating PN (day2), 48hr after initiating PN (day 3) and five days after initiating PN (day 6). These include full blood count (FBC), urea, creatinine & electrolytes, c-reactive protein (CRP), calcium, magnesium & phosphate, liver function tests (AST, ALT, GGT and total bilirubin), triglycerides, glucose & blood gases. Blood samples were collected at the same time each day via an arterial line and analysed on site.

Routine laboratory measurements were taken as part of the monitoring protocol for patients on PN. Electrolytes were corrected as per patients' individual requirements. Glycaemic control was managed according to ICU protocol. Based on the laboratory measurements the SOFA score and PaO_2/FiO_2 ratio were calculated daily.Once the blood samples were taken, the tubes were labelled with the study participant's name and the participant's hospital sticker was placed on the form.

b. Special blood samples for study

The additional special laboratory measurements were ordered by ticking a request form which indicated which special tests were requested on that day and the tubes needed, e.g. day 1: TNF-α and IL-1β, 1 yellow top tube 10ml (see Appendix AVII). The form, was a different colour to the routine laboratory request form, and was pre-packed in a specimen bag with all the tubes inside needed for the tests for that day. The specimen bags were labelled on the outside according to the day, e.g. day 1. This enabled the doctor and/or phlebotomist to know which bloods needed to be drawn on that particular day.

These samples were then centrifuged for 5 minutes at 4000rpm and stored at -80^0C.

Once the study was completed half of the stored, frozen blood samples were couriered to the Centre for TB Research, Division of Molecular Biology and Human Genetics, Faculty of Medicien

and Health Sciences, Stellenbosch University for analysis and the other half of frozen samples were couriered to the University of Potchefstroom, Nutrition Department for analysis of total plasma phospholipid fatty acids.

A total of 55ml of blood was needed for all the laboratory measurements on day 1, day 3 and day 6, i.e. 5ml whole blood for FBC and 2, 10ml yellow top tubes for the routine blood tests, 3, 10ml yellow top tubes for the cytokines and fatty acids test. On the other days 25ml of blood was needed for the tests.

Table 3-2: Additional laboratory measurements:

Test	Colour top tube	Day 1 (pre-PN)	Day 3 (48hr on PN)	Day 6 (120 hr on PN)	Handling procedure
TNF-α, IL-1 β, IL-6, IL-10, Fatty acids	2 yellow top tubes 10ml	✓	✓	✓	Centrifuge sample ,freeze at -20^{0}C and store at -80^{0}C

3.6.7 Logistics

All the study participants' data was collected by the research assistant at all sites. The whole process of the study was controlled by the primary study investigator. Weekly contact was made with the research assistant, and ICU dietitian, and daily contact with the pharmacist at Fresenius Kabi if a patient was on the study. WDGMC was visited three to five times per week to assist with data collection and patient recruitment, especially over weekends if special laboratory measurements were needed. The study investigator visited Bloemfontein quarterly.

The study investigator was responsible for the training of the research assistant, the pharmacist and locum at Fresenius Kabi Bloemfontein and Johannesburg as well as the ICU dietitian at all the sites. The hospital pharmacy was also informed about the study and their role was defined in the process. The study investigator actively communicated regularly with the NHLS laboratory at Universitas and Pelonomi, Prof Meiring at the department of Haematology, and Beverly Grose at BARC SA.

The study investigator was responsible for the quality control checks. The quality control form (see Appendix AVI), was be completed by the research assistant as well as the pharmacists at Fresenius Kabi Bloemfontein and Johannesburg, and kept separately. The case report forms were sent to the study investigator by the research assistant. These completed forms were placed in a sealed envelope and couriered to the study investigator at the end of each week, or collected from the site. The study investigator captured all the data once the forms were received.

3.7 Data management and statistics

The data was captured by the study investigator using Excel on a weekly basis. The data was backed up using a hard drive as well as a storage device. Only the research assistant and study investigator had access to the raw data. The participant's study number was used at all times to guarantee confidentiality. Any outlier values were checked by the study investigator. The final study data collected was kept in a locked cabinet in Midrand and only made available once the study had been closed.

3.7.1 Statistical Analysis of Data:

All data was analysed in consultation with Professor Nel, the allocated statistician at the University of Stellenbosch.

MS Excel was used to capture the data and STATISTICA version 13.2 (StatSoft Inc. (2016 STATISTICA (data analysis software system, www.statsoft.com.)) was used to analyse the data.

Summary statistics were used to describe the variables. Distributions of variables were presented with histograms and/or frequency tables. Medians or means were used as the measures of central location for ordinal and continuous responses and standard deviations and quartiles as indicators of spread.

The relationship between two continuous variables were analysed with regression analysis and the strength of the relationship measured with Pearson's correlation; or Spearman's correlation if the continuous variables were not normally distributed. If one continuous response variable was related to several other continuous input variables, multiple regression analysis was used and the strength of the relationship measured with multiple correlation.

The relationships between continuous response variables and nominal input variables (like different diets) were analysed using appropriate analysis of variance (ANOVA) and appropriate repeated measures analysis of variance (RMANOVA) when responses were measured at specific time intervals.

When ordinal response variables were compared versus a nominal input variable, non-parametric ANOVA methods was used. For completely randomised designs the Mann–Whitney test or the Kruskal–Wallis test was used and for repeated measures designs the Wilcoxon- or Friedman tests was used.

The relation between nominal variables was investigated with contingency tables and appropriate chi-square tests, namely the likelihood ratio chi-square test or the McNemar's test.

A p-value of $p < 0.05$ represented statistical significance in hypothesis testing and 95% confidence intervals was used to describe the estimation of unknown parameters.

3.7.2 Analysis of other data

Fluid input and output was analysed, as well as the contribution of energy and fat from Propofol and the energy contribution from other I.V fluids.

3.7.3 Biochemical data

The biochemical data that was recorded on a daily basis was entered into a database by the study investigator. Normal values for the different measurements was obtained from the laboratory and entered into the database. Standard cut off values were determined by the laboratory.

3.7.4 Nutrition status assessment

All the nutritional assessment criteria as defined by Appendix A was entered into the database.

3.7.5 Any other relevant data

The SOFA score, RIFLE criteria for renal failure, the patient's blood pressure, temperature as well as blood gases, particularly PaO_2/FiO_2 defined by Appendix A was entered into the database.

3.8 Ethical and legal aspects

The study protocol was approved by the Health Research Ethics Committee of Stellenbosch University on the 26th of March 2013, by the Ethics Committee of the University of the Free State on 4th March 2014 and by the Human Research Ethics Committee (Medical) of the University of Witwatersrand on 6th February 2015.

Permission was granted by Dr Galaejwe, head of clinical services Universitas Academic Hospital as well as Professor R S du Toit, head of department of surgery at Universitas Academic Hospital. Permission was also been granted from the director of clinical services at Pelonomi Hospital, Dr Benganga. Permission was granted by Dr Sue Tager (hospital hanager) and Dr Günter Schleicher (director of ICU) from WDGMC.

Consent was obtained from the study participant or his/her closest relatives. When the closest relatives were unable to give consent, the Clinical Manager at the site decided if the patient could be included into the study. This was in accordance to the standard practices of Universitas Hospital and WDGMC in the case of the patient being unable to consent. The Clinical Manager was independent from the daily patient management and assessed the research based on the study merits and the inclusion criteria. The patient was re-consented once possible and if the patient did not agree to continue participating in the study or did not want to give permission for his/her data to be used, the data was destroyed immediately. The study was conducted in accordance to Good Clinical Practice (GCP) guidelines as well as the declaration of Helsinki.

The study was registered on the South African National Clinical Trials Register database, registration number: DOH-27-0616-4323.

Only the research assistant and study investigator had access to the raw data. The participant's study number was used at all times to guarantee confidentiality.

CHAPTER 4

RESULTS

4. Introduction

The results chapter is discussed in the form of two manuscripts prepared for publication in two of the following journals: Critical Care Medicine or Clinical Nutrition or American Journal of Clinical Nutrition or Nutrition in Clinical Practice.

The first manuscript focuses on the effects of a fish oil (FO) containing intravenous lipid emulsion (IVLE) on inflammatory markers, gas exchange and clinical outcomes in patients with the systemic inflammatory response syndrome (SIRS) or sepsis. In this manuscript the results of the nutritional intake, laboratory parameters, cytokines analysis, gas exchange and clinical outcomes are addressed.

The second manuscript focuses on the effects of a FO containing IVLE on the plasma phospholipid fatty acid composition in septic patients, namely, oleic, linoleic, alpha-linolenic, myristic, and arachidonic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In this manuscript the results of nutritional intake, plasma total phospholipid fatty acid composition, dose of fish oil intake, omega-6:omega-3 polyunsaturated fatty acid ratio, and clinical outcomes are addressed.

Some additional results not included in either of the manuscripts are discussed in Section 4.3.

The study was initially planned to be a multicentre study including two centres in Bloemfontein, namely, the multi-disciplinary ICU and surgical ICU at Universitas Hospital and the ICU at Pelonomi Hospital. Recruitment at these centres started in June 2014; however it was very slow owing to challenges in the healthcare administration in the province and subsequently only 9 patients were recruited in 10 months. It was decided to open another centre at Wits Donald Gordon Medical Centre (WDGMC), Johannesburg, to continue with the study and to close the centres in Bloemfontein. Only the patients recruited from WDGMC were included in the two manuscripts.

A total of 400 adult ICU patients admitted to WDGMC were screened for eligibility between April 2015 and June 2016. Only 75 patients met the inclusion criteria and were randomised after obtaining consent. In the study group, four patients were excluded due to protocol violation (n=2), consent withdrawal (n=1) and insufficient biochemical results (n=1). In the control group three patients were excluded due to protocol violation (n=2) and withdrawn consent (n=1) (See Figure 1: Flow diagram of patient inclusion).

The commencement of enteral nutrition, as well as the calculation of nutrients, was not defined in the protocol. Enteral nutrition was started as soon as possible according to the hospital protocol and guidelines. The composition as well as the contribution of enteral nutrition was similar in both groups. The commencement of early enteral nutrition in nearly half the patients resulted in a reduced intake of parenteral FO in the Study group (SG) and a reduction in IV lipids in both groups.

4.1 MANUSCRIPT ONE

EFFECT OF A FISH OIL CONTAINING INTRAVENOUS LIPID EMULSION ON INFLAMMATORY MARKERS, GAS EXCHANGE AND CLINICAL OUTCOMES IN SEPTIC PATIENTS

EFFECT OF A FISH OIL CONTAINING INTRAVENOUS LIPID EMULSION ON INFLAMMATORY MARKERS, GAS EXCHANGE AND CLINICAL OUTCOMES IN SEPTIC PATIENTS

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Abstract:

Introduction

The effect of parenteral nutrition (PN) lipid emulsions containing omega-3 polyunsaturated fatty acid in critically ill patients has not been studied widely and shows conflicting results. This study compared the effects of a 4-oil lipid emulsion containing fish oil (SMOFlipid®) with a 100% soybean-based lipid emulsion in terms of biochemical parameters, inflammatory mediators, sequential organ failure assessment (SOFA) score, gas exchange, and clinical outcomes in ICU patients with the systemic inflammatory response syndrome (SIRS), with or without sepsis, or the acute respiratory distress syndrome (ARDS).

Design

Double-blind, randomised, single-centre study.

Method

Seventy-five patients predicted to need PN for five days or more were randomised to receive either a 4-oil lipid emulsion (Study Group (SG)) or a 100% soybean lipid emulsion (Control Group (CG)). Isocaloric, isonitrogenous PN was administered continuously over a period of 5 days. Routine haematological and biochemical measurements were performed and SOFA score assessment was calculated daily. Plasma cytokines were analysed on days 1, 3 and 6.

Results

The triglyceride levels increased significantly from day 1 to day 6, in both the SG and CG (p<0.001 for both groups); however the range was wider in the CG.

Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin improved in both treatment groups. The ALT levels decreased, whereas the gamma-glutamyl transferase (GGT) levels increased in both groups. There was a trend for a bigger decrease in ALT, AST and bilirubin levels from day 1 to day 6 in the SG. The biggest decrease in bilirubin occurred between day 1 and day 3 and continued to decrease in the SG, whereas levels increased significantly in the CG after

day 3 (p=0.039). Concentrations of TNF-α decreased from day 1 to day 6 in the SG, whereas they increased in the CG, but the change was not statistically significant (p=0.112). Concentrations of Interleukin-1β (IL-1β) and IL-6 decreased in the SG during the intervention and had a tendency to increase in the CG after day 3 (p=0.175 for IL-1β and p=0.056 for IL-6) but the difference was not significant. IL-10 concentrations decreased in both groups between day 1 and day 3, but then increased from day 3 to day 6 in the SG. This difference was not significant (p=0.972).

In the SG, a weak correlation was found between day 3 eicosapentaenoic acid (EPA) intake and bilirubin levels (r=-0.125, p=0.527), fewer days on mechanical ventilation (r=-0.201, p=0.224) and a reduction in C-reactive protein (CRP) levels (r=-0.027, p=0.097) and a significant correlation was found for improvement in the Sequential Organ Failure Assessment Score (SOFA) (r=0.4047, p=0.018). A weak correlation was also seen between day 6 fish oil (FO) intake and ICU length of stay (LOS) (r=-0.167, p=0.437).

Days on mechanical ventilation (1.24 ± 0.83 days in SG versus 0.88 ± 1.63 days in CG, p=0.385) and ICU LOS (9.5 ± 7.09 days in SG versus 10.7 ± 7.6 days in CG, p=0.49) were not different between the two groups. Even though the baseline APACHE score was higher in the SG, there was no difference in mortality between the groups.

Conclusion

This study results suggest that PN containing a 4-oil LE with FO at a dose of 0.09 – 0.22g/kg in ICU participants with SIRS, with or without sepsis, or ARDS, is safe and well tolerated in this patient population. The 4-oil LE showed a tendency to reduce plasma TNF-α, liver enzymes (ALT and bilirubin), SOFA score and ICU length of stay but no difference in mortality. Additional studies need to be done in this patient population paying particular attention to the dose, duration and timing of FO, EPA and n-6:n-3 PUFA ratio per day and their effect on clinical outcomes.

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Introduction

Sepsis remains a common problem in critically ill patients. The reported prevalence of the systemic inflammatory response syndrome (SIRS) is estimated to range from 20% to 60%. Approximately 40% of patients with sepsis may develop septic shock (1). Severe sepsis and septic shock have high mortality rates and are the leading causes of death in intensive care units (2). There is an increasing awareness that patients who survive sepsis often have long-term physical, psychological and cognitive disabilities with significant health care and social implications (3).

In most patients, critical illness starts with varying degrees of physiological deterioration, developing into a catabolic state and intense metabolic changes, resulting in malnutrition and impaired immune functions (4). Intravenous lipid emulsions (IVLEs) constitute the main source of energy and fatty acids (FAs) in parenteral nutrition (PN) formulations and are associated with the development of adverse effects. Different types of lipid emulsions (LEs) have different effects on blood function tests and metabolic functions. Clinical data in surgical and critical care patients suggest that the addition of fish oil lipid emulsions (FO LEs) at 0.1 – 0.2g/kg/day (with omega-3 polyunsaturated FA (PUFAs) to PN attenuates the inflammatory process by reducing pro-inflammatory cytokines and maintaining concentrations of anti-inflammatory cytokines, improves oxygenation by increasing PaO_2/FiO_2 ratio, and reduces the incidence of parenteral nutrition-associated liver disease (PNALD) by having less derangement of liver enzymes. These changes have been shown to improve clinical outcomes such as reduction in time on mechanical ventilation and in ICU, and hospital length of stay (LOS) (5-8).

The aim of this study was to compare a 4-oil lipid emulsion containing fish oil (SMOFlipid®) with a 100% soybean-based lipid emulsion in terms of specified clinical and biochemical parameters, inflammatory mediators in plasma, SOFA score, gas exchange, and clinical outcome, in ICU patients with SIRS, with or without sepsis, or ARDS, requiring PN for five days or more. Our hypothesis is that inclusion of fish oil will decrease circulating inflammatory cytokine concentrations, improve gas exchange, and improve clinical outcomes.

Materials and Methods

Study design

This study was a double-blind, single-centre, randomised controlled trial in adult patients admitted to Wits Donald Gordon Medical Centre (WDGMC) ICU with diagnosed SIRS or sepsis and ARDS.

Sample size

The total number of study participants needed was determined to be at least 72 individuals (36 in each subgroup). This number was calculated using a power analysis for ANOVA with two groups,

significance level of 0.05 and an effect size of 0.55. Sample size *n*=36 in each group was expected to yield 90% power to detect this effect size.

A total of 75 patients were included in the study, and seven patients were excluded due to insufficient biochemical results, protocol violations and withdrawn consent, leaving a total of 68 patients. Thirty-five patients were randomised to the study group versus 33 patients to the control group (Figure 1).

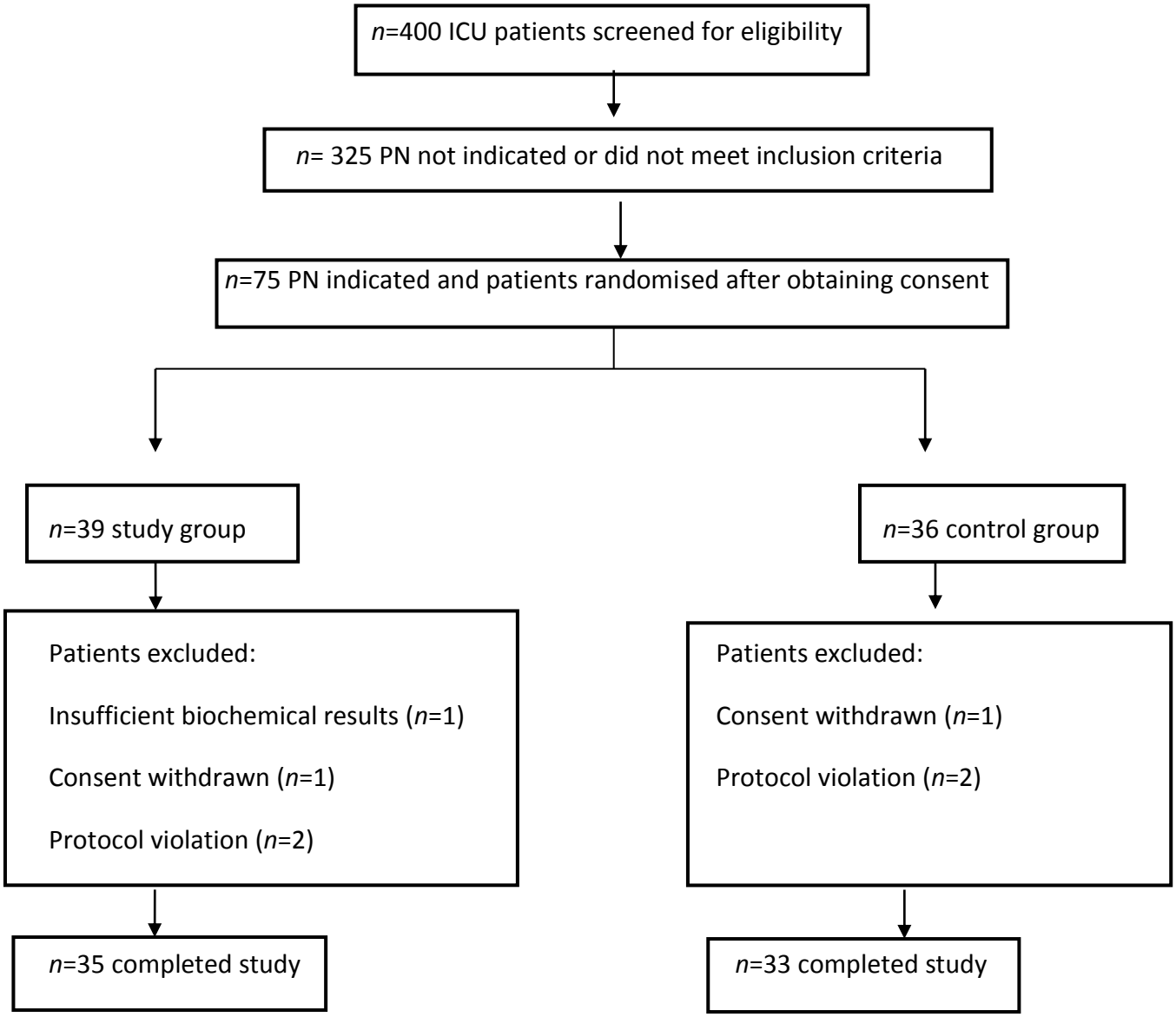

Figure 1: Flow diagram of patient inclusion

Patient selection

Seventy-five adult (18 years or older) patients with diagnosed SIRS, with or without sepsis, or ARDS, who were predicted to need PN for 5 days or more were recruited consecutively at the time of admission to the ICU between April 2015 and June 2016. Seven patients were excluded leaving a total of 68 patients. Sepsis was defined as suspected or proven infection plus SIRS (that is, presence of pyrexia, tachycardia, tachypnoea and/or leukocytosis). Severe sepsis was defined as sepsis with organ dysfunction (hypotension, hypoxaemia, oliguria, metabolic acidosis and/or thrombocytopaenia). Septic shock was defined as severe sepsis with hypotension despite adequate fluid resuscitation (9, 10).

The exclusion criteria were as follows: younger than 18 years, on full enteral feeding, pregnancy, treatment with immunosuppressive drugs, treatment with hydrocortisone >300mg/day at admission, plasma triglycerides >4,52mmol/l (>400mg/dl), chronic liver disease and/or acute hepatitis, chronic renal failure and/or end-stage renal disease according to the RIFLE criteria, recent stroke and known allergic reaction to fish or egg proteins confirmed by previous medical history.

Once the patient was identified as eligible and consent was obtained, the dietitian calculated the APACHE II and SOFA scores and nutritional assessment was performed. A PN prescription was then recommended to the clinician, taking laboratory results into account. The PN was ordered from Fresenius Kabi, Johannesburg (the supplier of the PN). On receiving the PN prescription, the dispensing pharmacist was responsible for randomising all the patients to either receive PN containing a 4-oil lipid emulsion including fish oil (SMOFlipid®: 30% LCT, 30% MCT, 25% olive oil, 15% fish oil, provided in a complete all-in-one PN bag by Fresenius Kabi: study group) or a soybean-based lipid emulsion (Intralipid® 100% LCT, provided in a complete all-in-one PN bag by Fresenius Kabi: control group), according to a randomisation sheet.

The dispensed PN bags looked identical. The PN was started on the day after admission to the study. By following the above procedure there was no deviation from usual standardised PN prescription techniques, the only difference being in the fat composition of the bags. (Refer to Table 1.) All the patient information was recorded daily until discharge from ICU.

Table 1: Composition of the parenteral nutrition bags

Contents of PN **Per 1000ml**	Study group PN Code : ITN 8807	Control group PN Code : ITN 8007
Total energy	929 kcal	929 kcal
Energy (NPE)	753 kcal	753 kcal
Carbohydrates	84g (45% of NPE)	84g (45% of NPE)
Fat Soybean oil MCT Olive oil Fish oil EPA + DHA n-6:n-3 fatty acid ratio	42g (55% of NPE) 12.6g 12.6g 10.5g 6.3g 1.9g 2.5:1	42g (55% of NPE) 42g 0 0 0 0 7:1
Nitrogen	7g	7g
Glutamine	6.3g	6.3g
Vitamins, minerals and trace elements	RDA	RDA
Osmolarity	981mOsm/l	978mOsm/l
Abbreviations: NPE: Non-Protein Energy; RDA: Recommended Daily Allowance; MCT: Medium-Chain Triglycerides; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid		

Anthropometric assessment

Weight and height were determined or estimated on admission according to acknowledged procedures and used to calculate body mass index (BMI) (weight (kg)/height m^2).

Dietary intervention

Energy and protein requirements were calculated individually using the American Society of Parenteral and Enteral Nutrition (ASPEN) and European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines (25 – 30kcal/kg/day total energy (TE) and protein 1.2g – 2g/kg/day)(11, 12). All study participants received glutamine, vitamins, minerals, trace elements and electrolytes as part of the complete PN. The PN bags, in SG or CG, were prescribed according to study participant requirements and the administration rate was adjusted accordingly.

The commencement of enteral nutrition (EN) was not defined in the protocol and was started as soon as possible according to hospital protocol and guidelines. The nutritional requirements were recalculated to ensure that the nutritional intake did not exceed the requirements and to avoid overfeeding.

Laboratory measurements

All blood samples were collected on admission, immediately prior to starting the PN (day 1), 24 h after initiating PN (day 2), 48 h after initiating PN (day 3) and five days after initiating PN (day 6), included full blood count (FBC), urea, creatinine & electrolytes, c-reactive protein (CRP), calcium, magnesium & phosphate, liver function tests (AST, ALT, GGT and total bilirubin), triglycerides, glucose & blood gases. Blood samples were collected at the same time each day via an arterial line and analysed on site. The 6ml blood required for cytokine levels was taken on day 1, 3 and 6 at the same time as the routine bloods. These samples were centrifuged and stored at -80 ^{0}C until analysed.

Routine laboratory measurements were taken as part of the monitoring protocol for patients on PN. Electrolytes were corrected as per patients' individual requirements. Based on the laboratory measurements, the SOFA score and PaO_2/FiO_2 ratio were calculated daily.

Cytokine analysis

Cytokine levels (TNF-α, IL-1α, IL-6 & IL-10) were measured using MILLIPLEX® kits (Merck Millipore, Billerica, MA, USA) on the MAGPIX® instrument according to the Milliplex instructions. All samples were evaluated in duplicate by a single technician who was blinded to participant groups. All analyte levels in the quality-control reagents included in the kits were within the expected ranges. All median fluorescent intensity data were acquired using the Bio Plex MP™ software (Bio-Rad, Hercules, CA, USA) and analysed on the Bio Plex manager version 6.1 software (Bio-Rad) (13). The

cytokine levels were measured at the Centre for TB Research, Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University.

Statistical analysis

STATISTICA version 13.2 (StatSoft Inc. (2016) STATISTICA (data analysis software system, www.statsoft.com) was used to analyse the data.

Summary statistics were used to describe the variables. Distributions of variables were analysed with histograms and/or frequency tables. Medians or means were used as the measures of central location for ordinal and continuous responses and standard deviations or quartiles as indicators of spread.

Descriptive statistical analysis was performed to evaluate the result of the laboratory parameters, cytokines, PaO_2/FiO_2 ratio and clinical data for each variable at day 1, day 3 and day 6.

The relationships between nutritional intake, TG, liver enzymes, PaO_2/FiO_2 ratio, cytokines, SOFA score, ICU mortality and nutritional efficacy and type of PN were analysed using appropriate analysis of variance (ANOVA) and appropriate repeated measures analysis of variance (RMANOVA), when responses were measured at day 1, day 3 and day 6.

Results were compared using the Mann–Whitney test or the Kruskal–Wallis test for ordered categorical counts in case of non-paired data. In case of paired data, the Wilcoxon or Friedman tests were used.

The relationship between two continuous variables was analysed with regression analysis and the strength of the relationship measured with Pearson's correlation coefficient or Spearman's correlation coefficient if the continuous variables were not normally distributed or if the input was ordinal. The relation between nominal variables was investigated with contingency tables and appropriate chi-square tests, namely the likelihood ratio chi-square test or McNemar's test.

A p-value of $p < 0.05$ represented statistical significance in hypothesis testing and 95% confidence intervals were used to describe the estimation of unknown parameters.

Ethics and legal aspects

The study was approved by the Health Research Ethics Committee of Stellenbosch University and the Human Research Ethics Committee (Medical) of the University of the Witwatersrand. Permission was granted by the hospital manager and the director of the ICU at WDGMC. Consent was obtained from the study participant or his/her closest relatives. The study was conducted in accordance with the Helsinki Declaration and was registered on the South African National Clinical Trials Register database, registration number: DOH-27-0616-4323.

Results

Of the 68 participants, 66% were male and 34% female in the SG versus 56% male and 45% female in the CG (p=0.333). The majority of the participants were surgical admissions (85% in SG versus 91% in CG) and the remainder were medical admissions. The average age was 60.8 ± 13.9 years in SG versus 55.7 ± 14.8 years in CG.

On admission to the study, the baseline characteristics of the participants in the two groups did not differ (Table 2).

Nutrient intakes

Total energy, protein, fat, carbohydrate and glutamine intakes did not differ between the groups throughout the study period (Table 3), except on day 3, the energy provided per kilogram body weight was significantly more in the CG (p=0.041). The SG fish oil (FO) intake was between 0.09 ± 0.03g/kg/day (day 1) and 0.22 ± 0.11g/kg/day (day 3), providing between 1.15 ± 0.44 to 2.37 ± 0.79g EPA and 1.72 ± 0.42 to 2.18 ± 0.44g DHA per day. The EPA and DHA intake was the highest on day 3. The phytosterol intake was significantly more in the CG (p=0.008) and α-tocopherol intake was significantly more in the SG (p<0.001).

EN was started on days 4.03 ± 2.1 in the SG versus 3.64 ± 1.90 in CG (p=0.42). The nutritional intake from EN was documented, but the nutritional value not calculated accurately owing to missing data. Thus, the nutrient intake tabulated on day 6 was less than that of day 3, as it only included intake from PN. Table 3 includes only nutritional intake from PN.

Only 63% of participants in the SG and 54% in CG received PN for 6 days, and the cumulative FO intake was significantly more in the SG participants that received PN for 6 days compared with those who received PN for fewer days (p=0.032).

Laboratory measurements

There were no statistically significant differences between the groups with regard to white cell count (WCC), blood glucose, triglycerides, liver enzymes and total bilirubin (Table 4) throughout the study period. Assessing the groups individually, the triglyceride levels increased from day 1 to day 6, in both groups (p<0.001 for SG and CG); however the range was wider in the CG (Fig. 2).

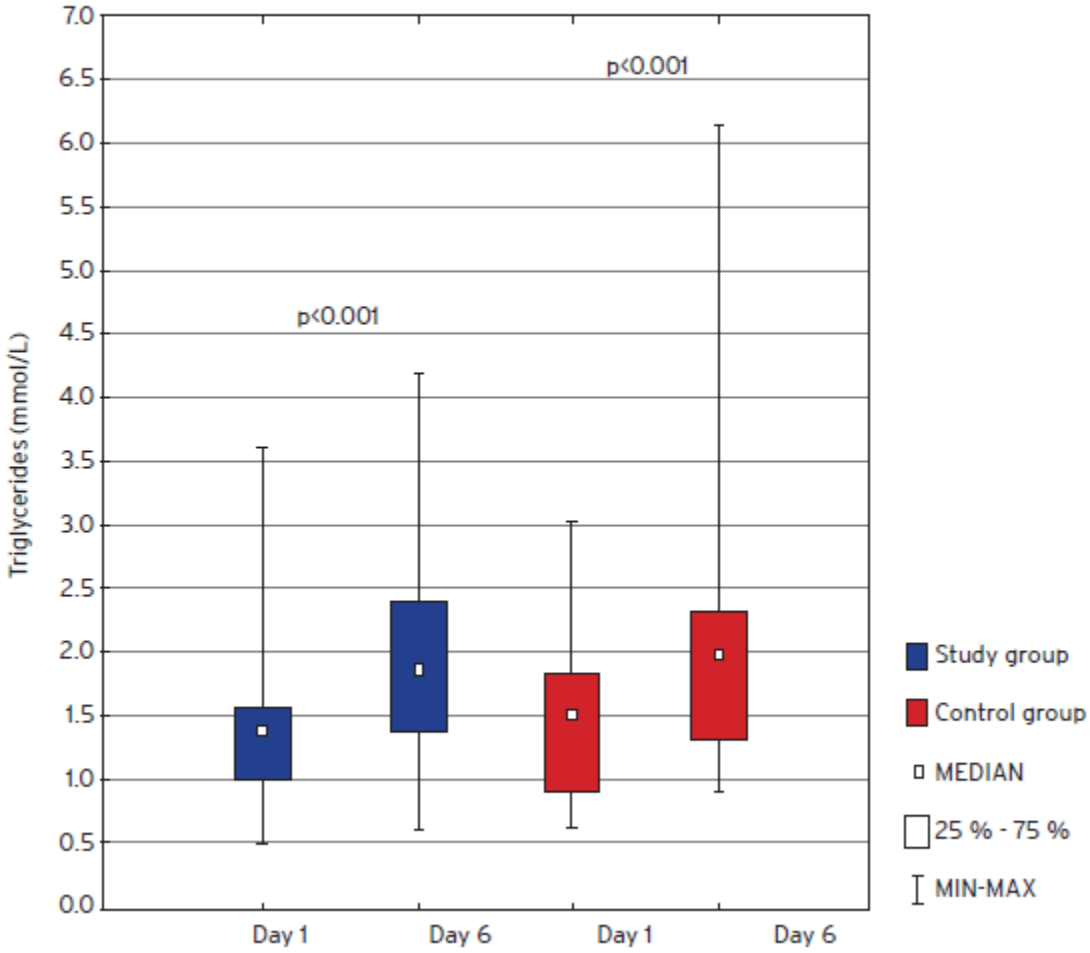

Figure 2: Differences in triglycerides on day 1 and day 6 in both treatment groups

AST, ALT and bilirubin improved in both groups (Table 4). The ALT levels decreased whereas the GGT levels increased in both groups. There was a trend for a bigger decrease in ALT, AST and bilirubin levels from day 1 to day 6 in the SG. The biggest decrease in bilirubin occurred between day 1 and day 3 and remained fairly stable after day 3 in the SG, whereas levels increased in the CG after day 3 (Figure 3). The difference between the levels in both groups on day 6 was significant (p=0.039). A weak, negative correlation was found between day 3 EPA intake and levels (r=-0.125, p=0.527).

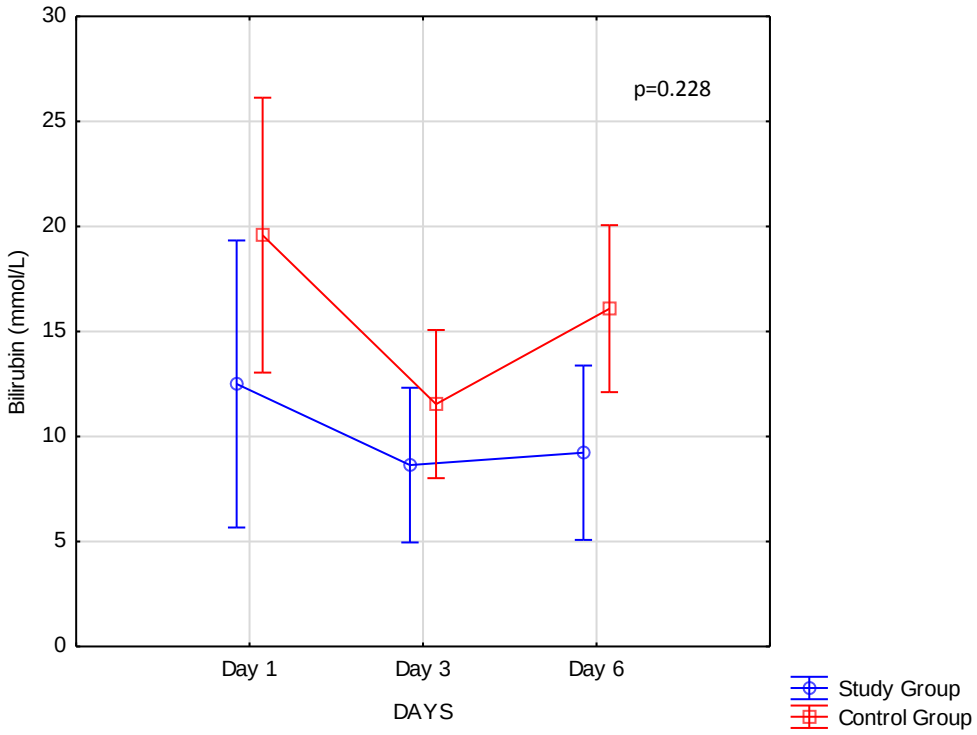

Figure 3: Overall change in bilirubin levels between the two groups (*p*=0.228)

Table 2: Baseline characteristics of participants in the two treatment groups

	Study Group (*n*=35)			Control Group (*n*=33)			Comparison between SG & CG
Characteristic	**Mean ± SD**	**-95%LCL**	**+95% UCL**	**Mean ± SD**	**-95%LCL**	**+95% UCL**	***p* value**
Age	60.77 ± 13.93	56.19	65.35	55.71 ± 14.78	50.46	60.95	*p*=0.142
BMI kg/m^2	29.2 ± 11.01	25.47	32.93	27.57 ± 5.91	25.48	29.67	*p*=0.452
APACHE II score	13.65 ± 7.47	11.08	16.21	11.15 ± 8.08	8.27	14.02	*p*=0.190
SOFA score	5.66 ± 4.01	4.28	7.036	5.06 ± 4.17	3.558	6.57	*p*=0.554
Temperature (^{0}C)	36.97 ± 1.18	36.58	37.36	36.79 ± 0.81	36.50	37.07	*p*=0.453
Heart rate	95.53 ± 22.91	88.00	103.06	97.88 ± 14.68	92.67	103.09	*p*=0.614
WCC (10^9 cells/L)	13.60 ± 8.68	10.75	16.46	17.36 ± 12.89	12.79	21.93	*p*=0.150
CRP (mg/L)	205.17 ± 127.3	161.44	248.9	220.52 ± 129.14	172.30	268.74	*p*=0.632
Albumin (g/L)	25.85 ± 5.65	23.85	27.85	25.84 ± 5.48	23.83	27.85	*p*=0.994
PaO_2/FiO_2 ratio	279.41 ± 139.33	231.55	327.27	314.8 ± 107.63	275.99	353.6	*p*=0.252

BMI: body mass index; SOFA: Sequential Organ Failure Assessment; WCC: white cell count; PaO_2/FiO_2: partial pressure arterial oxygen to fractional inspired oxygen; LCL: lower confidence limit; UCL: upper confidence limit

Table 3: Nutritional intake from parenteral nutrition

	Study Group (*n*=35)			Control Group (*n*=33)			
	Day 1	**Day 3**	**Day 6**	**Day 1**	**Day 3**	**Day 6**	**Comparison between SG & CG**
Nutritional intake	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	***p* value**
Energy (kcal)	1130.82 ± 429.26	2249.87 ± 386.1	1132.45 ± 1034.46	1034 ± 430.18	2222.6 ± 352.41	1176.13 ± 984.67	*p*=0.357* *p*=0.758** *p*=0.858***
Energy (kcal/kg)	14.3 ± 5.64	25.69 ± 8.61	14.46 ± 13.44	13.85 ± 5.69	29.39 ± 5.85	15.463 ± 13.28	*p*=0.712* *p*=0.041** *p*=0.754***
Protein (g/kg)	0.67 ± 0.26	1.33 ± 0.16	0.68 ± 0.64	0.65 ± 0.25	1.39 ± 0.2	0.7 ± 0.61	*p*=0.74* *p*=0.157** *p*=0.914***
Glutamine (g/kg)	0.09 ± 0.03	0.18 ± 0.03	0.09 ± 0.1	0.09 ± 0.03	0.2 ± 0.07	0.09 ± 0.09	*p*=0.873* *p*=0.230** *p*=0.862***
Fat (g/kg)	0.63 ± 0.24	1.26 ± 0.16	0.65 ± 0.59	0.624 ± 0.24	1.32 ± 0.19	0.66 ± 0.57	*p*=0.892* *p*=0.188** *p*=0.877***
Carbohydrate (g/kg)	1.36 ± 0.61	2.58 ± 0.34	1.34 ± 1.27	1.3 ± 0.62	2.8 ± 0.59	1.47 ± 1.27	*p*=0.675* *p*=0.05** *p*=0.651***
Fish oil (g/kg)	0.09 ± 0.03	0.22 ± 0.11	0.14 ± 0.06				
EPA (g)	1.15 ± 0.44	2.37 ± 0.47	1.75 ± 0.79				
DHA (g)	1.72 ± 0.42	2.18 ± 0.44	1.61 ± 0.72				
Phytosterol (mg)	48.76 ± 18.26	102.35 ± 20.16	52.23 ± 45.41	96.15 ± 33.39	205.98 ± 34.19	99.83 ± 92.78	*p*<0.001* *p*<0.001** *p*=0.009***
a-tocopherol (mg)	48 ± 17.67	100.04 ± 17.88	50.95 ± 45.56	9.85 ± 8.69	18.49 ± 3.1	8.93 ± 8.29	*p*<0.001* *p*<0.001** *p*<0.001***

* Difference between groups on day 1 ** Difference between groups on day 3 *** Difference between groups on day 6 EPA; Eicosapentaenoic acid, DHA; Docosahexaenoic acid

Table 4: Laboratory measurements on day 1, day 3 and day 6

	Study Group (n=35)			Control Group (n=33)			Comparison between SG & CG
	Day 1	Day 3	Day 6	Day 1	Day 3	Day 6	
Measurement	**Mean ± SE**	**Mean ± SE**	**Mean ± SE**	**Mean ± SD**	**Mean ± SE**	**Mean ± SE**	**P value**
TG (mmol/L)	1.47 ± 0.11	1.1.78 ± 0.17	1.99 ±0.19	1.44 ± 0.11	2.27 ± 0.17	2.17 ± 0.18	p=0.035
AST (IU/L)	73.36 ± 15.73	35.3 ± 4.35	35.9 ± 5.01	53.9 ± 16.23	33.13 ± 4.49	38.84 ± 5.17	P=0.377
ALT (IU/L)	45.84 ± 9.23	32.90 ± 8.18	20.13 ± 2.53	28.9 ± 9.38	26.83 ± 8.31	17.7 ± 2.58	p=0.377
GGT (IU/L)	76.79 ± 18.01	68.89 ± 12.38	126.96 ± 23.39	75.86 ± 17.7	67.35 ± 12.17	150.41 ± 22.98	p=0.571
Bilirubin (mmol/L)	12.5 ± 3.39	8.64 ± 1.83	9.22 ± 2.05	19.58 ± 3.25	11.54 ± 1.75	16.08 ± 1.97	p=0.228
PaO_2/FiO_2 ratio	285.79 ± 25.39	228.51 ± 22.51	254.02 ± 25.01	319.3 ± 29.5	293.25 ± 26.15	305 ± 29.07	p=0.769
WCC (10^9 cells/L)	14.16 ± 1.97	12.1 ± 1.39	14.84 ± 1.67	17.85 ± 2.03	14.24 ± 1.44	14.99 ± 1.73	p=0.37
Glucose (mmol/L)	7.44 ± 0.33	8.44 ± 0.35	7.75 ± 0.48	6.79 ± 0.35	8.54 ± 0.36	7.92 ± 0.5	p=0.483

TG: triglyceride; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; PaO_2/FiO_2: partial pressure arterial oxygen to fractional inspired oxygen; WCC: white cell count

Table 5: Changes in cytokines from day 1, day 3 and day 6

	Study Group (*n*=35)			Control Group (*n*=33)			
	Day 1	**Day 3**	**Day 6**	**Day 1**	**Day 3**	**Day 6**	**Comparison between SG & CG**
Measurement	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	***p* value**
CRP (mg/L)	205.17 ± 127.3	169 ± 101.36	109.6 ± 69.7	220.52 ± 129.1	145.84 ± 73.57	119.05 ± 82.41	*p*=0.632* *p*=0.292** *p*=0.631***
TNF – α (pg/ml)	8.84 ± 15.11	3.62 ± 5.76	5.09 ± 10.81	5.27 ± 11.55	8.92 ± 21.97	8.59 ± 21.03	*p*=0.301* *p*=0.205** *p*=0.428***
IL-1β (pg/ml)	2.79 ± 10.01	2.38 ± 8.78	0.98 ± 3.21	0.167 ± 0.45	0.146 ± 0.41	0.18 ± 0.50	*p*=0.151* *p*=0.156** *p*=0.175***
IL-6 (pg/ml)	101.24 ± 238.47	26.93 ± 42.82	11.53 ±28.42	125.76 ± 343.3	32.16 ± 76.1	41.8 ± 78.8	*p*=0.749* *p*=0.742** *p*=0.056***
IL-10 (pg/ml)	98.36 ± 353.03	23.66 ± 34.95	35.98 ±102.5	103.95± 444.8	37.54 ± 88.51	35.12 ± 86.23	*p*=0.957* *p*=0.426** *p*=0.972***

* Difference between groups on day 1 ** Difference between groups on day 3 *** Difference between groups on day 6

CRP: c-reactive protein; TNF-α: tumour necrosis factor – alpha; IL-1β: interleukin-1β; IL-6: interleukin-6; IL-10: interleukin-10

Table 6: Clinical outcome measurements day 1 and day 6

	Study Group						**Control Group**						
	Day 1			**Day 6**			**Day 1**			**Day 6**			**Comparison between SG & CG**
	Mean ± SE	**-95% LCL**	**+95% UCL**	**Mean ± SE**	**-95% LCL**	**+95% UCL**	**Mean ± SE**	**-95% LCL**	**+95% UCL**	**Mean ± SE**	**-95% LCL**	**+95% UCL**	***p* value**
SOFA	5.77 ± 0.75	4.26	7.28	4.27 ± 0.77	2.72	5.82	5.91 ± 0.86	4.191	7.635	3.83 ± 0.88	2.06	5.6	*p*=0.578
CRP (mg/L)	199.82 ± 23	153.74	245.9	103.6 ± 13.9	75.71	131.46	215.47 ± 23.4	168.56	262.37	116.99 ± 14.16	88.62	145.36	*p*=0.951
TNF-α (pg/ml)	9.45 ± 2.53	4.38	14.52	5.09 ± 3.12	-1.16	11.34	4.95 ± 2.49	-0.03	9.93	8.59 ± 3.06	2.44	14.73	*p*=0.122

SOFA: Sequential Organ Failure Assessment; CRP: c-reactive protein; TNF-α: tumour necrosis factor – alpha; LCL: lower confidence limit; UCL: upper confidence limit

Gas exchange

There was no statistical difference in the PaO_2/FiO_2 ratio between the two groups (Table 4). A non significant positive correlation was found between the intake of EPA on day 3 and the improvement in PaO_2/FiO_2 ratio (r=0.237, p=0.192).

Plasma cytokine concentrations

Plasma cytokine concentrations did not differ statistically between the two groups prior to initiation of PN and throughout the study period. Concentrations of TNF-α decreased from day 1 to day 6 in the SG, whereas they increased in the CG, but the change was not statistically significant (Fig. 4). Concentrations of IL-1β and IL-6 decreased in the SG during the intervention and had a tendency to increase in the CG on day 6; however the difference was not statistically significant. IL-10 concentrations decreased in both groups; however in the SG on day 6 the concentration increased but not significantly (Table 5). A positive, non-significant correlation was found between the FO intake and the concentrations of IL-10 (r=0.232, p=0.082).

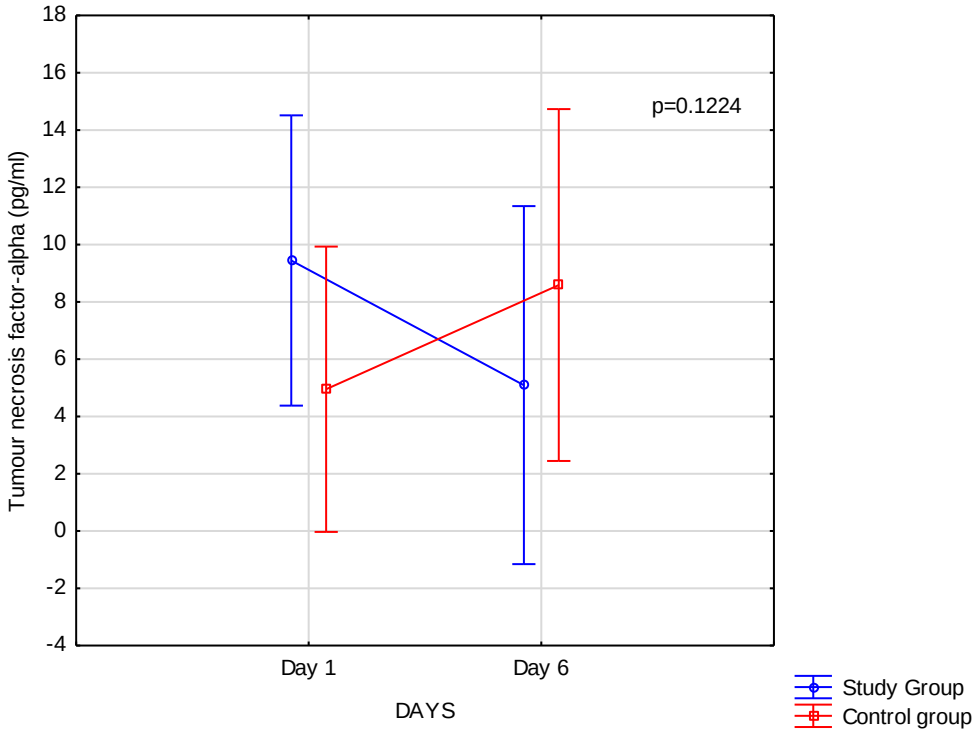

Figure 4: Plasma tumour necrosis factor-α concentration

Clinical outcomes

As expected the CRP levels decreased in both groups during the intervention. A weak negative correlation was shown between the intake of EPA on day 3 and the reduction in CRP levels (r= -0.029, p=0.097). Days on mechanical ventilation (1.24 ± 0.83 days in SG vs 0.88 ± 1.63 days in CG, p=0.385) and ICU LOS (9.5 ± 7.09 days in SG vs 10.7 ± 7.6 days in CG, p=0.49) were not different between the two groups; however the SG has a shorter ICU LOS.

Even though the baseline mean APACHE score was higher in the SG (p=0.19), there was no difference in mortality between the two groups (p= 0.071). Two participants died within the course of the intervention from neutropenic sepsis, both in the SG. A further nine participants died after the completion of the intervention period but before day 28 (five from the SG and four from the CG. The SOFA score improved in both treatment groups during the intervention as expected (Table 6). A strong negative correlation was found between day 3 EPA intake and day 3 SOFA score (r=-0.4047, p=0.018) (see Fig. 5). A non-significant negative correlation was also shown for day 3 EPA intake and days on mechanical ventilation (r=-0.201, p=0.224) as well as between day 6 FO intake and ICU LOS (r=-0.167, p=0.437).

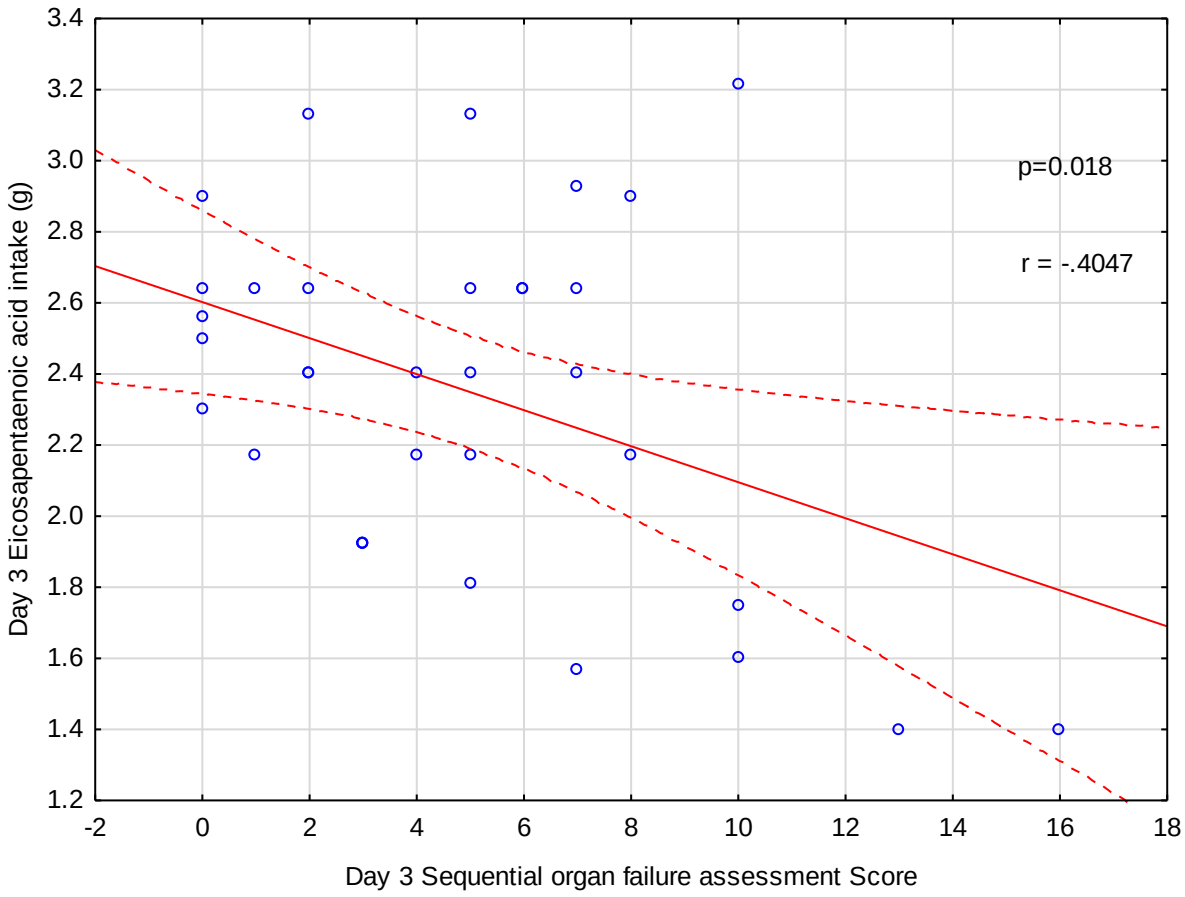

Figure 5: Correlations between day 3 eicosapentaenoic acid intake and day 3 sequential organ failure assessment score

Discussion

This study set out to compare a 4-oil LE containing FO (SMOFlipid®) with a 100% soybean-based LE in terms of routine biochemical and physiological markers, gas exchange, inflammatory mediators, SOFA score and clinical outcomes in ICU participants with SIRS, with or without sepsis, or ARDS. It found a significant increase in α-tocopherol and a decrease in phytosterol intake but no statistical difference in inflammatory cytokines, liver enzymes, SOFA score, and length of ICU stay. Even though the mean baseline APACHE score was higher in the SG, there was no difference in mortality between the two groups.

EN was started on day 4 in the SG versus day 3.6 in the CG and only 63.2% of participants in the SG and 54.5% in CG received PN for the full six days. The cumulative FO intake was significantly more in the SG between the participants that received PN for 6 days versus those that received it over fewer days (p=0.032). The maximum intake of FO, EPA and DHA was on day 3. Day 3 EPA intake was associated with improved bilirubin levels, fewer days on mechanical ventilation, a reduction in CRP levels, and a significant improvement in SOFA score.

To our knowledge this is the first randomised controlled study using SMOFlipid® in septic ICU participants, although it has been studied previously in post-surgery participants (14-21). In these studies SMOFlipid® was found to decrease production or concentration of inflammatory cytokines and eicosanoids (15, 21), decrease liver enzymes (14, 16, 18), increase plasma α-tocopherol (14, 15) and reduce length of hospital stay (15).

Other FO containing LEs have also been studied in post-surgical participants where they decreased production or concentration of inflammatory eicosanoids and cytokines (22-24), improved immune function, reduced liver enzymes (23, 25) and improved clinical outcomes (24-29).

These other FO containing LEs have also been studied in critically ill and septic participants (30-34). In some of these studies the use of FO containing LE was associated with decreased inflammatory markers and improved respiratory function (30) and significant reduction in nosocomial infections and prolonged predicted time free of infection (31). Heller et al. (32) used an FO supplement in a heterogeneous group of participants including trauma, post-surgical and septic participants and identified a dose-dependent (0.1–0.2g/kg) reduction in mortality, infection rate and length of stay. A recent study by Grau-Carmona et al. showed a shorter length of mechanical ventilation and hospital stay in the FO group but it was not statistically significant (31). However, other studies reported no effect on mortality and length of stay (2, 33).

The dose of fish oil administered in this study ranged between 0.09 – 0.22g/kg and is consistent with the dose that other studies have found to be clinically favourable (31, 32, 34). The highest dose of FO was on day 3 as EN was started afterwards and resulted in a reduction in PN intake and FO intake.

This study did not demonstrate a statistical difference between the PaO_2/FiO_2 ratio on day 1 and day 6 between the two groups, which has been demonstrated previously (23, 30). This could be due to the fact that the optimal dose of FO was only received for 2 days.

Plasma cytokines did not differ statistically in this study between the two groups; however plasma levels of TNF-α decreased in the SG and increased in the CG. Similar results were shown in surgical participants with an FO supplement and SO vs SO alone (24, 35), and FO supplement plus MCT/LCT vs MCT/LCT alone (22). Kreymann et al. found no clear-cut effect on TNF-α levels in both FO admixtures and FO-supplemented LE (36).

A recent meta-analysis confirmed a significant reduction in infection rates by 35% in critically ill participants with no overall effect on ICU LOS. They concluded that FO admixtures and FO supplement LEs are advantageous for the majority of participants compared with LCT or MCT/LCT LE owing to their balancing omega-3 content (36).

Adverse reactions did not differ between groups and no serious or unexpected adverse events were reported, confirming the findings of a variety of clinical trials that PN containing FO is safe in critically ill participants (30, 31, 32, 33, 34, 37).

Nutritional efficacy was similar between the two groups. However, the intake of α-tocopherol was significantly higher and phytosterol significantly lower in the SG. There is evidence that large intakes of phytosterols can cause cholestasis and PN-associated liver disease (7). This study showed a non significant reduction in liver enzymes, particularly ALT and bilirubin in the SG.

The limitations of this study are that only half the participants received PN for the full six days; this affected the duration as well as the dose of FO over the study period. There was a definite signal that the intake of EPA and FO on day 3 showed a beneficial effect. It was not possible to determine the full nutritional intake throughout the study period owing to the incomplete recording of EN intake. Infection rate as well as days on antibiotics was also not documented and would have provided valuable information about clinical outcomes. The study population may have been somewhat heterogenous as to the causes and severity of SIRS and ARDS. Finally, we were unable to test plasma α-tocopherol levels, which would have been an interesting additional result as the intake was significantly different between the two groups.

Conclusion

This study results suggest that PN containing a 4-oil LE with FO at a dose of 0.09 – 0.22g/kg in ICU participants with SIRS, with or without sepsis, or ARDS, is safe and well tolerated in this patient population. The 4-oil LE showed a tendency to reduce plasma TNF-α, liver enzymes (ALT and bilirubin), SOFA score and ICU length of stay but no difference in mortality. Additional studies need to be done in this patient population paying particular attention to the dose, duration and timing of FO, EPA and n-6:n-3 PUFA ratio per day and their effect on clinical outcomes.

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4.2 MANUSCRIPT TWO

EFFECT OF A FISH OIL CONTAINING INTRAVENOUS LIPID EMULSION ON THE PLASMA FATTY ACID COMPOSITION IN SEPTIC PATIENTS

EFFECT OF A FISH OIL CONTAINING INTRAVENOUS LIPID EMULSION ON THE PLASMA FATTY ACID COMPOSITION OF SEPTIC PATIENTS

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Abstract:

Introduction

The effect of intravenous lipid emulsions, containing omega-3 polyunsaturated fatty acid in Parenteral Nutrition (PN) has not been studied widely in critically ill patients and shows conflicting results. This study compared the effects of a 4-oil lipid emulsion (30% soybean oil, 30% medium-chain triglycerides, 25% olive oil and 15% fish oil) (SMOFlipid®) with a 100% soybean-based lipid emulsion in terms of routine biochemical parameters, plasma total phospholipid fatty acid (FA) composition; organ dysfunction, and clinical outcomes in patients with the systemic inflammatory response syndrome (SIRS), with or without sepsis, or the acute respiratory distress syndrome (ARDS) in intensive care units (ICUs).

Design

This was a double-blind, randomised, single-centre study.

Method

Seventy-five patients predicted to need PN for more than 5 days were randomised to receive either a 4-oil lipid emulsion (Study Group (SG)) or a 100% soybean lipid emulsion (Control Group (CG)). Isocaloric, isonitrogenous PN was administered continuously for 5 days. Routine biochemical measurements were assessed. Sequential organ failure assessment (SOFA) score was calculated and the plasma total phospholipid FA composition was analysed.

Results

The nutritional intakes did not differ, except the SG received fish oil (FO), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as well as increased amounts of α-tocopherol and reduced amounts of phytosterols. The highest intake of FO, EPA and DHA was on day 3, as EN was started on approximately day 4 in both groups. Multiple changes in plasma total phospholipid FA percentages were demonstrated. Oleic acid (p=0.022) and alpha-linolenic acid (p<0.0005)

increased in both groups. Plasma EPA showed a significant increase in the SG (p<0.000), whereas DHA increased after day 3. DHA levels decreased in the CG resulting in a difference between the two groups on day 6 (p<0.001). Arachidonic acid decreased in both groups. The omega-6:omega-3 polyunsaturated fatty acid (n-6:n-3 PUFA) ratio decreased in the SG and remained fairly constant in the CG.

A weak correlation was found between EPA intake on day 3 and fewer days on mechanical ventilation (r=-0.201, p=0.224) and a reduction in C-reactive protein (CRP) levels (r=-0.027, p=0.097) and a significant improvement in SOFA score (r=0.4047, p=0.018). Days on mechanical ventilation (1.24 ± 0.83 days in SG versus 0.88 ± 1.63 days in CG, p=0.385) and ICU LOS (9.5 ± 7.09 days in SG versus 10.7 ± 7.6 days in CG, p=0.49) were not different between the two groups. Even though the mean baseline APACHE II score was higher in the SG, there was no difference in mortality between the groups (p=0071).

Conclusion

The results of this study suggest that PN containing a 4-oil LE with FO at a dose of 0.09 – 0.22g/kg in adult ICU patients with SIRS, with or without sepsis, or ARDS, showed multiple changes in the plasma total phospholipid FA profile. Both plasma EPA and DHA increased significantly in the SG. The n-6:n-3 PUFA ratio decreased in the SG and remained fairly constant in the CG. The 4-oil LE appears to be safe and well tolerated. There was no significant difference in terms of CRP, SOFA, length of ICU stay and mortality. Additional studies need to be done in this patient population, paying particular attention to the dose, duration and timing of FO, EPA and n-6:n-3 PUFA ratio per day and their effect on clinical outcomes.

Introduction

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, characterised by a catabolic state and intense metabolic changes, resulting in malnutrition and impaired immune functions (1).

Sepsis remains a common problem in critically ill patients. According to a worldwide survey, 29.5% of patients had sepsis on admission or during the Intensive care unit (ICU) stay. ICU mortality rates were 25.8% in patients with sepsis (2). There is an increasing awareness that patients who survive sepsis often have long-term physical, psychological and cognitive disabilities with significant health care and social implications (3).

Nutrition therapy 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 (4). The enteral route is preferable and should be commenced once the patient

is haemodynamically stable (5). Where enteral nutrition (EN) is impossible or not tolerated, parenteral nutrition (PN) (either as total or supplementary) may safely be administered (6).

Intravenous lipid emulsions (IVLEs) constitute the main source of energy and FAs in parenteral nutrition formulations. However, they are also associated with the development of adverse effects (7).

FAs 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) (7, 8). 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 (7, 9). Changing the FA composition of cells involved in the inflammatory response influences their functions. The anti-inflammatory effects of n-3 PUFAs suggest that they may be useful as therapeutic agents in disorders with an inflammatory component (10).

The metabolites of n-3 PUFAs, primarily from EPA and DHA, compete with arachidonic acid (AA) (from n-6 PUFA) for use of the same enzymes, cyclooxygenase and lipoxygenase (11, 12). Fish oil (FO) has high concentrations of EPA and DHA, and 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-tocopheral, which is added to prevent the oxidation of its fatty acids (12, 13). Based on experimental and clinical studies, the most favourable n-6:n-3 PUFA ratio is proposed to range between 2:1 and 4:1 (14-17).

There is clinical data suggesting that n-3 PUFAs, particularly fish oil (0.1 – 0.2g/kg/day), has beneficial effects on the immune system, organ function and improves clinical outcomes in surgical and ARDS patients. In addition, there is some promising data on their use in septic patients (8, 9, 17, 18).

The aim of this study was to compare a 4-oil lipid emulsion (30% soybean oil (SO), 30% medium-chain triglycerides (MCTs), 25% olive oil (OO) and 15% fish oil (FO)) (SMOFlipid®) with a 100% soybean-based lipid emulsion in terms of certain outcomes (routine biochemical parameters, total phospholipid plasma fatty acid composition and clinical outcome) in patients with SIRS, with or without sepsis, or ARDS in ICU, requiring parenteral nutrition (PN) for more than 5 days. It was hypothesised that inclusion of FO would increase plasma EPA, modify plasma total phospholipid fatty acid profile and improve clinical outcomes. This specific article addresses the impact of intravenous FO on changes in plasma EPA and fatty acid composition. The rest of the results from this study are available in Donoghue et al. (19).

Materials and Methods

Study design

This study was a single-centre, double-blind, randomised controlled trial in ICU patients admitted to Wits Donald Gordon Medical Centre (WDGMC) ICU with diagnosed SIRS or sepsis and ARDS.

Sample size

The total number of study participants needed was determined to be at least 72 individuals (36 in each subgroup). This number was calculated using a power analysis for ANOVA with two groups, significance level of 0.05 and an effect size of 0.55. Sample size n=36 in each group was expected to yield 90% power to detect this effect size.

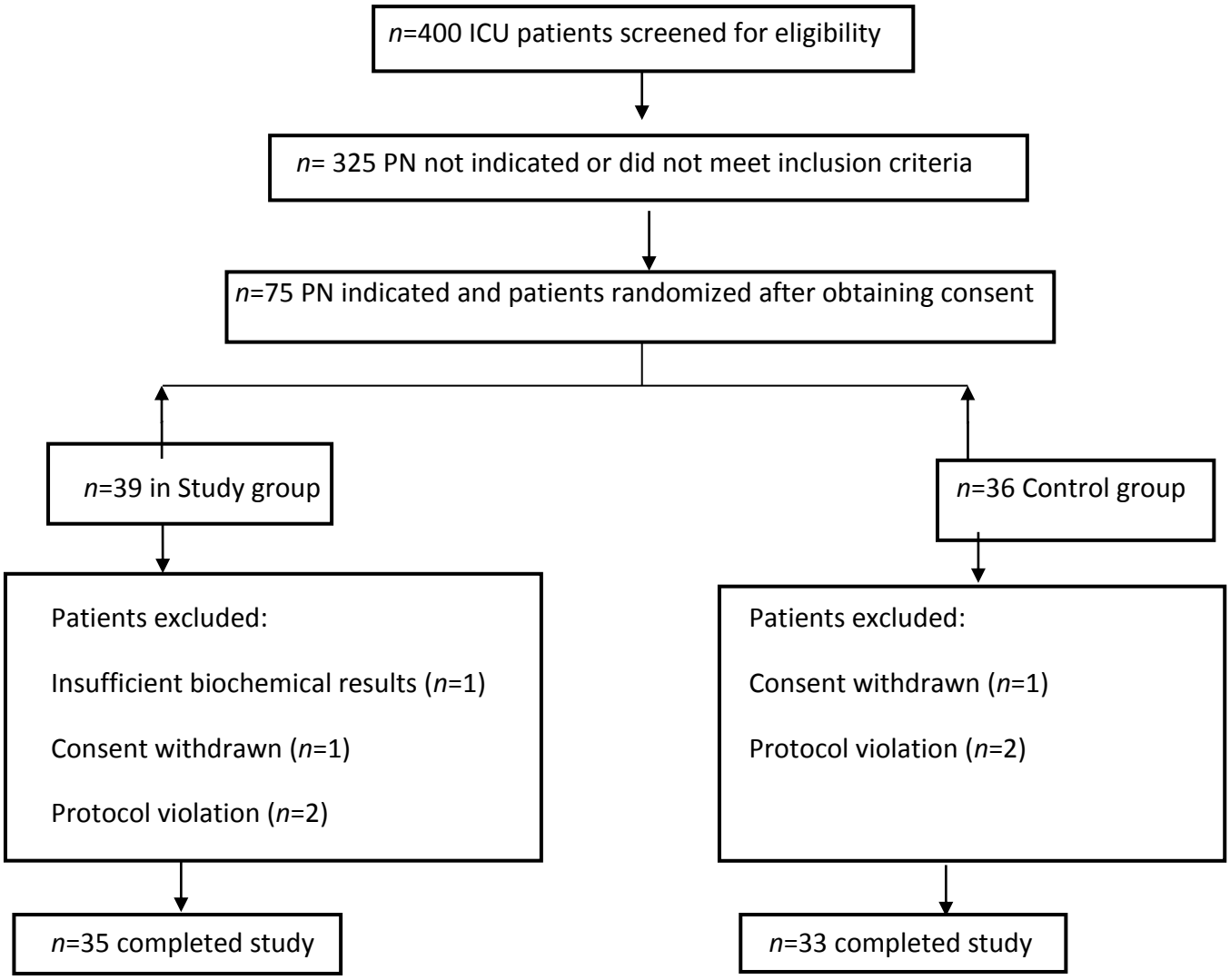

Figure 1: Flow diagram of patient inclusion

Patient selection

A total number of 75 adult patients were included in the study; seven patients were excluded due to insufficient biochemical results, protocol violation and withdrawn consent, leaving a total of 68 patients. Thirty-five patients were in the study group (SG) versus 33 patients in the control group (CG) (Fig. 1).

Adult patients diagnosed with SIRS or sepsis and ARDS who were predicted to need PN for more than 5 days were included consecutively at the time of admission to the ICU. Patients were recruited between April 2015 and June 2016. Sepsis was defined as suspected or proven infection plus SIRS (that is, presence of pyrexia, tachycardia, tachypnoea and/or leukocytosis). Severe sepsis was defined as sepsis with organ dysfunction (hypotension, hypoxaemia, oliguria, metabolic acidosis and/or thrombocytopaenia). Septic shock was defined as severe sepsis with hypotension despite adequate fluid resuscitation (20, 21).

The exclusion criteria were as follows: <18 yr old, on full enteral feeding, pregnancy, treatment with immunosuppressive drugs or treatment with hydrocortisone >300mg/day at admission, plasma triglycerides >4,52mmol/l (>400mg/dl), chronic liver disease or acute hepatitis, RIFLE stage III and IV renal failure, recent stroke and known allergic reaction to fish or egg proteins confirmed by previous medical history.

The full methodology of this study is discussed in another unpublished article (223). In short, after consent was obtained, patients were randomised according to a randomisation sheet to received either PN containing a 4-oil lipid emulsion (SMOFlipid®: 30% LCT, 30% MCT, 25% olive oil, 15% fish oil, provided in a complete all-in-one PN bag by Fresenius Kabi: Study Group) or a soybean-based lipid emulsion (Intralipid® 100% LCT, provided in a complete all-in-one PN bag by Fresenius Kabi: Control Group). Only the fat composition was different (refer to Table 1), otherwise the bags were identical.

Table 1: The composition of the parenteral nutrition bag

Contents of PN **Per 1000ml**	Study group PN Code : ITN 8807	Control group PN Code : ITN 8007
Total Energy	929 kcal	929 kcal
Energy (NPE)	753 kcal	753 kcal
Carbohydrates	84g (45% of NPE)	84g (45% of NPE)
Fat Soybean oil MCT Olive oil Fish oil EPA + DHA n-6:n-3 fatty acid ratio	42g (55% of NPE) 12.6g 12.6g 10.5g 6.3g 1.9g 1	42g (55% of NPE) 42g 0 0 0 0 7:1
Nitrogen	7g	7g
Glutamine	6.3g	6.3g
Vitamins, minerals and trace elements	RDA	RDA
Osmolarity	981mOsm/l	978mOsm/l
Abbreviations : NPE: Non-Protein Energy; RDA: Recommended Daily Allowance; MCT: Medium-Chain Triglycerides; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid		

Anthropometric assessment

Weight and height were determined or estimated according to acknowledged procedures. Body Mass Index (BMI) was calculated on admission using estimated weight (kg)/height in m^2 and used to classify patients as undernourished, normal, overweight or obese (5, 22).

Dietary intervention

The American Society of Parenteral and Enteral Nutrition (ASPEN) and European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines (25 – 30kcal/kg/day total energy (TE) and protein 1.2g – 2g/kg/day) were used to calculate energy and protein requirements (5,22). Both groups of study participants received micronutrients, glutamine and electrolytes as part of the complete PN. The PN bags in the SG or CG were prescribed according to the study participants' nutritional and fluid requirements and the administration rate was adjusted accordingly.

The commencement of enteral nutrition (EN) was not defined in the protocol and was started as soon as possible according to guidelines and hospital protocol. The nutritional requirements were recalculated when EN was started to ensure that the nutritional intake did not exceed the requirements and to avoid overfeeding.

Laboratory measurements

All blood samples were collected on admission, immediately prior to starting the PN (day 1), 24h after initiating PN (day 2), 48h after initiating PN (day 3) and five days after initiating PN (day 6). These included full blood count (FBC), urea, creatinine & electrolytes, c-reactive protein (CRP), calcium, magnesium & phosphate, liver function tests (AST, ALT, GGT and total bilirubin), triglycerides, glucose & blood gases. Blood samples were collected at the same time each day via an arterial line and analysed on site. The 6ml blood required for plasma total phospholipid fatty acids were taken on day 1, 3 and 6 at the same time as the routine bloods. These samples were centrifuged and stored at -80 ^{0}C until analysed.

Routine biochemical measurements were taken as part of the monitoring protocol for patients on PN. Electrolytes were corrected as per patients' individual requirement. Glycaemic control was managed according to ICU protocol. Based on the laboratory measurements, the SOFA score was calculated daily.

Plasma total phospholipid fatty acid composition analysis

Total phospholipid fatty acid composition analysis in plasma was performed within 18 months after collection. The detailed method was described in a previous publication (24). Fatty acids were analysed by using quadrupole gas chromatography-electron impact-mass spectrometry on an Agilent Technologies 7890A Gas Chromatograph system equipped with an Agilent Technologies 5975C VL mass selective detector (Agilent Technologies). The gas chromatography separation of fatty acid methyl esters (FAMEs) was carried out on a BPX 70 capillary column (60 m 3 0.25 mm; SGE Analytical Science) by using helium as the carrier gas at a flow rate of 1.3 mL/min.

Quantitation of FAME was performed by using the selected ion-extraction method on the basis of the response of two diagnostic ions. FAME peaks were identified and calibrated against a standard reference mixture of 33 FAMEs (Nu-Chek Prep) and two single FAME standards (Larodan Fine Chemicals AB). Relative percentages of fatty acids were calculated by taking the concentration of a given fatty acid derivative as a percentage of the total concentration of all fatty acids identified in the sample. This analysis was conducted at the Department of Nutrition, North-West University, Potchefstroom campus.

Statistical analysis

Statistical analyses were performed using STATISTICA version 13.2 (StatSoft Inc. (2016) STATISTICA (data analysis software system, www.statsoft.com).

Summary statistics were used to describe the variables. Distributions of variables were analysed with histograms and/or frequency tables. Medians or means were used as the measures of central location for ordinal and continuous responses and standard deviations or quartiles as indicators of spread.

Evaluations of the results of the nutritional intake, laboratory parameters, total plasma phospholipid FA and clinical data were performed by descriptive statistical analysis for each variable and at day 1, day 3 and day 6. Baseline was defined as the data obtained before the intervention. Endpoints were defined as net change of post intervention from baseline.

The relationship between total plasma phospholipid FA and the treatment groups was analysed with regression analysis and the strength of the relationship measured with Pearson's correlation coefficient or Spearman's correlation coefficient if the continuous variables were not normally distributed.

The fatty acid composition of the SG and the CG were compared using appropriate analysis of variance (ANOVA) and appropriate repeated measures analysis of variance (RMANOVA) when responses were measured at day 1, day 3 and day 6. For completely randomised designs the Mann–Whitney test or the Kruskal–Wallis test was used and for repeated measures designs the Wilcoxon or Friedman tests were used.

The relation between nominal variables was investigated with contingency tables and appropriate chi-square tests, namely the likelihood ratio chi-square test or the McNemar test.

A p-value of $p < 0.05$ represented statistical significance in hypothesis testing and 95% confidence intervals were used to describe the estimation of unknown parameters.

Ethics and legal aspects

The study was approved by the Health Research Ethics Committee of Stellenbosch University and the Human Research Ethics Committee (Medical) of the University of Witwatersrand. Permission was granted by the director of the ICU and the hospital manager at WDGMC. Consent was obtained from the study participant or his/her closest relatives. The study was conducted in accordance with the Helsinki Declaration and was registered on the South African National Clinical Trials Register database, registration number: DOH-27-0616-4323.

Results

A total number of seventy-five patients were included in the study; however after the exclusion of seven patients, a total of 68 patients remained. Thirty-five patients were in the study group (SG) versus 33 patients in the control group (CG) (Fig. 1). Patients were followed up for 5 days after PN was commenced. On admission to the study the baseline characteristics of the patients in the two treatment groups did not differ (Table 2).

The gender distribution was 66% male and 34% female in the SG vs 56% male and 45% female in the CG (p=0.334). The average age was 60.8 ± 13.9 years in SG vs 55.7 ± 14.8 in CG. The majority of the participants were surgical admissions (85% in SG vs 91% in CG) and the remainder were medical admissions.

Nutritional intakes

Total energy, protein, fat, carbohydrates and glutamine intakes did not differ between the groups throughout the study period (Table 3), except on day 3 the energy provided per kilogram body weight was significantly more in the CG (p=0.041). The SG received FO ranging between 0.09 ± 0.03g/kg/day (minimum) and 0.22 ± 0.11g/kg/day (maximum), providing between 1.15 ± 0.44g to 2.37 ± 0.79g EPA and 1.72 ± 0.42g to 2.18 ± 0.44g DHA per day. The total FO intake ranged from 7.2g ± 2.7 to 15 ± 2.7g. The phytosterol and α-tocopherol intake were significantly different between the groups over the entire study period (p=0.008 and p<0.001 respectively).

EN was started on day 4.03 ± 2.1 in the SG versus day 3.64 ± 1.9 in CG (p=0.42). Unfortunately the nutritional intake from EN was not documented, especially oral intake. Thus, the nutrient intake tabulated on day 6 was less than that of day 3, as it only included intake from PN. Please note that Table 3 only includes nutritional intake from PN.

Only 63% of patients in the SG and 54% in the CG received PN for the full 6 days, and the cumulative FO intake was significantly more in the SG patients that received PN for 6 days compared with those who received PN for fewer days (p=0.032).

Laboratory measurements

There were no differences between the treatment groups with regard to white cell count (WCC), blood glucose, triglycerides, liver enzymes and total bilirubin (results in unpublished article (19)). The increase from baseline in triglycerides from day 1 to day 6 was significant in both groups (p<0.001 for SG and CG); however there was a trend for lower triglyceride levels in the SG.

Plasma total phospholipid fatty acids composition

The five-day infusion of a 4-oil LE in the SG providing 0.09 – 0.22g FO/kg/day resulted in multiple changes in the plasma total phospholipid FA composition (Table 4). Baseline plasma FA compositions were similar between the two treatment groups except for lower linoleic acid (LA, p=0.008) and higher arachidonic acid (AA, p=0.005) levels in the SG.

Oleic acid (OA) percentages increased from day 1 to day 3 in both groups, and then remained fairly constant until day 6. OA was higher in the SG than in the CG on day 6 (p=0.022) (Table 4). The percentages of LA increased from day 1 to day 3 in the CG and then remained fairly constant. LA decreased in the SG (17.34 ± 3.37 on day 1 to 15.05 ± 2.14 on day 6). The differences in LA levels between the two groups were significant throughout the study period (Fig. 2A & B).

Alpha linolenic acid (ALA) increased significantly in both groups (p=0.004); however the increase was greater in the CG. AA decreased in both treatment groups: the decrease in the SG occurred throughout the study period, whereas the decrease in the CG occurred between day 1 and day 3 and then remained fairly constant until day 6. The difference between the two groups was significant (p=0.005) (Fig. 2C & D).

Myristic acid (MA) levels were similar in both groups at baseline. The levels increased in the SG from day 1 to day 6 and only increased in the CG from day 3 to day 6. On day 3 the MA levels were significantly different (p=0.003) in both groups; however on day 6 (p=0.054) the difference was no longer significant (Fig. 2E).

EPA increased significantly in the SG: the biggest increase was from day 1 to day 3 and it continued to increase up to day 6 (Fig. 2F). DHA remained fairly constant in the SG and increased slightly after day 3 but decreased in the CG. The difference between the two groups was significant (p<0.000)(Fig. 2G).

The plasma n-6 PUFA:n-3 PUFA ratio at baseline was similar between the two groups. This ratio decreased in the SG (5.61 ± 1.8 day 1 to 2.84 ± 0.73 day 6) and remained fairly constant in the CG (6.38 ± 2.1 day 1 to 6.52 ± 1.81 day 6). In comparing the two groups, the ratio was different on day 3 and day 6 (Table 4) (p=<0.000).

Clinical outcomes

CRP levels decreased in both groups during the intervention as expected. A correlation was shown between the intake of EPA on day 3 and the reduction in CRP levels (r=-0.029, p=0.097). Days on mechanical ventilation (1.24 ± 0.83 days in SG versus 0.88 ± 1.63 days in CG) and length of stay (LOS) in the ICU (9.5 ± 7.09 days in SG versus 10.7 ± 7.6 days in CG) were not different between the two groups (p=0.49); (Fig. 3). The SOFA score improved in both treatment groups during the intervention (Table 5). The positive significant correlation between day 3 EPA intake and day 3 SOFA score (r=-0.4047, p=0.018) (Fig. 4) was noted. A correlation was also shown for EPA intake on day 3 and fewer days on mechanical ventilation (r=-0.201, p=0.224).

Even though the mean baseline APACHE II score was higher in the SG (p=0.19), there was no difference in mortality (p=0.024).

Table 2: Baseline characteristics of patients in two treatment groups

	Study Group (*n*=35)			**Control Group (*n*=33)**			**Comparison between SG & CG group**
Characteristic	**Mean ± SD**	**-95% LCL**	**+95% UCL**	**Mean ± SD**	**-95% LCL**	**+95% UCL**	***p* value**
Age	60.77 ± 13.93	56.19	65.35	55.71 ± 14.78	50.46	60.95	*p*=0.143
BMI kg/m2	29.2 ± 11.01	25.47	32.93	27.57 ± 5.91	25.48	29.67	*p*=0.452
APACHE II Score	13.65 ± 7.47	11.08	16.21	11.15 ± 8.08	8.27	14.02	*p*=0.190
SOFA Score	5.66 ± 4.014	4.28	7.04	5.06 ± 4.17	3.56	6.57	*p*=0.554
Temperature	36.97 ± 1.18	36.58	37.36	36.79 ± 0.81	36.50	37.07	*p*=0.454
Heart Rate	95.53 ± 22.91	88.00	103.06	97.88 ± 14.68	92.67	103.09	*p*=0.614
WCC (10^9 cells/L)	13.6 ± 8.68	10.75	16.46	17.36 ± 12.89	12.79	21.93	*p*=0.150
C-reactive Protein	205.17 ± 127.3	161.44	248.9	220.52 ± 129.14	172.30	268.74	*p*=0.632
Albumin (g/L)	25.85 ± 5.65	23.85	27.85	25.84 ± 5.48	23.83	27.85	*p*=0.994

BMI: body mass index; SOFA: Sequential Organ Failure Assessment; WCC: white cell count; LCL: lower confidence limit; UCL: upper confidence limit

Table 3: Nutritional intake from parenteral nutrition

	Study Group (*n*=35)			**Control Group (*n*=33)**			
	Day 1	**Day 3**	**Day 6**	**Day 1**	**Day 3**	**Day 6**	**Comparison between SG & CG**
Nutritional intake	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	***p* value**
Energy (kcal)	1130.82 ± 429.26	2249.87 ± 386.1	1132.45 ± 1034.46	1034 ± 430.18	2222.6 ± 352.41	1176.13 ± 984.67	*p*=0.357* *p*=0.758** *p*=0.858***
Energy (kcal/kg)	14.3 ± 5.64	25.69 ± 8.61	14.464 ± 13.44	13.854 ± 5.69	29.39 ± 5.85	15.46 ± 13.28	*p*=0.712* *p*=0.041** *p*=0.754***
Protein (g/kg)	0.67 ± 0.26	1.33 ± 0.16	0.68 ± 0.64	0.65 ± 0.25	1.39 ± 0.2	0.70 ± 0.61	*p*=0.74* *p*=0.157** *p*=0.914***
Glutamine (g/kg)	0.09 ± 0.03	0.18 ± 0.03	0.09 ± 0.1	0.09 ± 0.03	0.2 ± 0.07	0.09 ± 0.09	*p*=0.873* *p*=0.230** *p*=0.862***
Fat (g/kg)	0.63 ± 0.24	1.26 ± 0.16	0.65 ± 0.59	0.62 ± 0.24	1.32 ± 0.19	0.66 ± 0.57	*p*=0.892* *p*=0.188** *p*=0.877***
Carbohydrate (g/kg)	1.36 ± 0.61	2.58 ± 0.34	1.34 ± 1.27	1.3 ± 0.62	2.80 ± 0.59	1.47 ± 1.27	*p*=0.675* *p*=0.05** *p*=0.651***
Fish oil (g)	7.2 ± 2.65	15 ± 2.68	11.2 ± 4.84				
Fish oil (g/kg)	0.09 ± 0.03	0.19 ± 0.03	0.14 ± 0.06				
EPA (g)	1.15 ± 0.44	2.372 ± 0.47	1.75 ± 0.79				
DHA (g)	1.72 ± 0.42	2.18 ± 0.44	1.61 ± 0.72				
Phytosterol (mg)	48.76 ± 18.3	102.35 ± 20.2	52.23 ± 45.41	96.15 ± 33.4	205.98 ± 34.2	99.83 ± 92.8	*p*<0.001* *p*<0.001** *p*=0.009***
a-tocopherol (mg)	48 ± 17.7	100.04 ± 17.9	50.95 ± 45.6	9.85 ± 8.7	18.49 ± 3.1	8.93 ± 8.29	*p*<0.001* *p*<0.001** *p*<0.001***

* Difference between groups on day 1 ** Difference between groups on day 3 *** Difference between groups on day 6

EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid

Table 4: Plasma total phospholipid fatty acids composition on day 1, day 3 and day 6

	Study Group (n=29)			Control Group (n=30)			
Measurement	**Day 1**	**Day 3**	**Day 6**	**Day 1**	**Day 3**	**Day 6**	**Comparison between SG & CG**
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	***p* value**
Oleic acid	9.71 ± 2.25	11.95 ± 2.33	11.89 ± 2.51	9.7 ± 1.83	10.94 ± 2.08	10.44 ± 2.03	*p*=0.98 *p*=0.086** *p*=0.022***
Linoleic acid	17.34 ± 3.37	16.28 ± 2.63	15.05 ± 2.14	19.7 ± 3.22	21.47 ± 3.87	20.66 ± 3.15	*p*=0.008* *p*<0.001** *p*<0.001***
Alpha linolenic acid	0.09 ± 0.06	0.15 ± 0.07	0.18 ± 0.09	0.12 ± 0.13	0.29 ± 0.15	0.34 ± 0.21	*p*=0.243* p<0.001** p<0.001***
Arachidonic acid	14.78 ± 3.16	12.55 ± 2.09	11.28 ± 1.59	13.25 ± 2.61	11.47 ± 2.9	11.64 ± 2.57	*p*=0.048* *p*=0.108** *p*=0.053***
Myristic acid	0.24 ± 0.08	0.29 ± 0.08	0.36 ± 0.13	0.23 ± 0.07	0.23 ± 0.05	0.30 ± 0.11	*p*=0.45* *p*=0.003** *p*=0.054***
Eicosapentaenoic acid	0.66 ± 0.56	2.07 ± 0.77	3.42 ± 0.95	0.55 ± 0.35	0.54 ± 0.42	0.94 ± 0.8	*p*=0.36* *p*<0.001** *p*<0.001***
Docosahexaenoic acid	5.11 ± 1.58	5.09 ± 1.16	5.86 ± 1.19	4.4 ± 1.38	4.07 ± 1.19	3.74 ± 1.31	*p*=0.071* *p*=0.017** *p*<0.001***
n-6:n-3 fatty acid ratio	5.61 ± 1.8	4.03 ± 0.97	2.84 ± 0.73	6.38 ± 2.1	6.67 ± 1.79	6.52 ± 1.81	*p*=0.137 *p*<0.001** *p*<0.001***

* Difference between groups on day 1 ** Difference between groups on day 3 *** Difference between groups on day 6

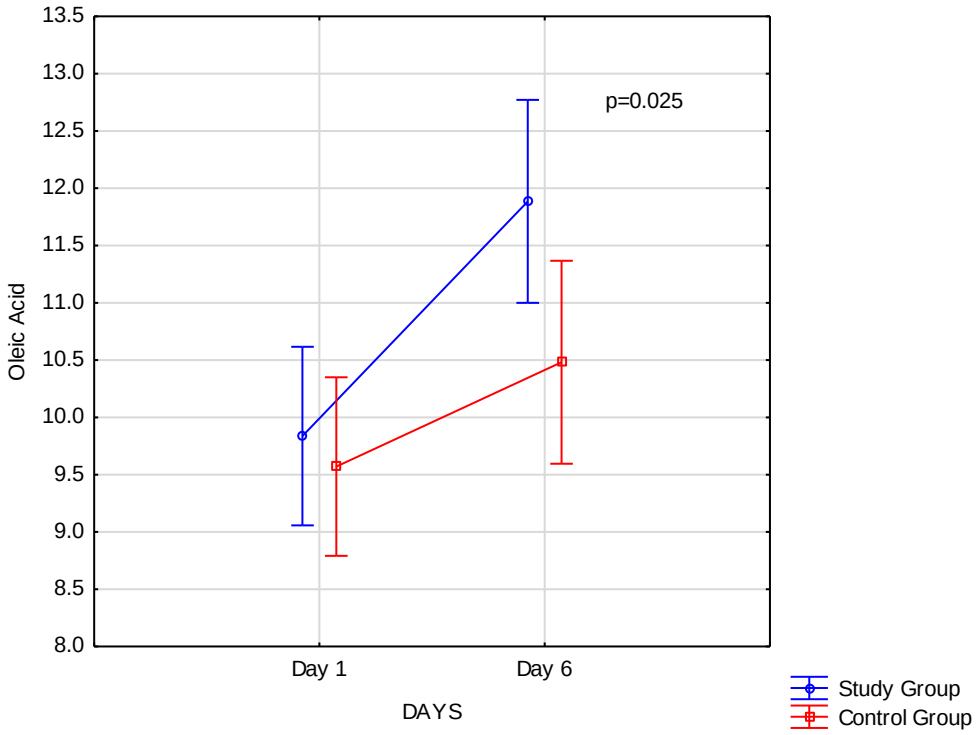

Figure 2A: Change in oleic acid per group over the study period

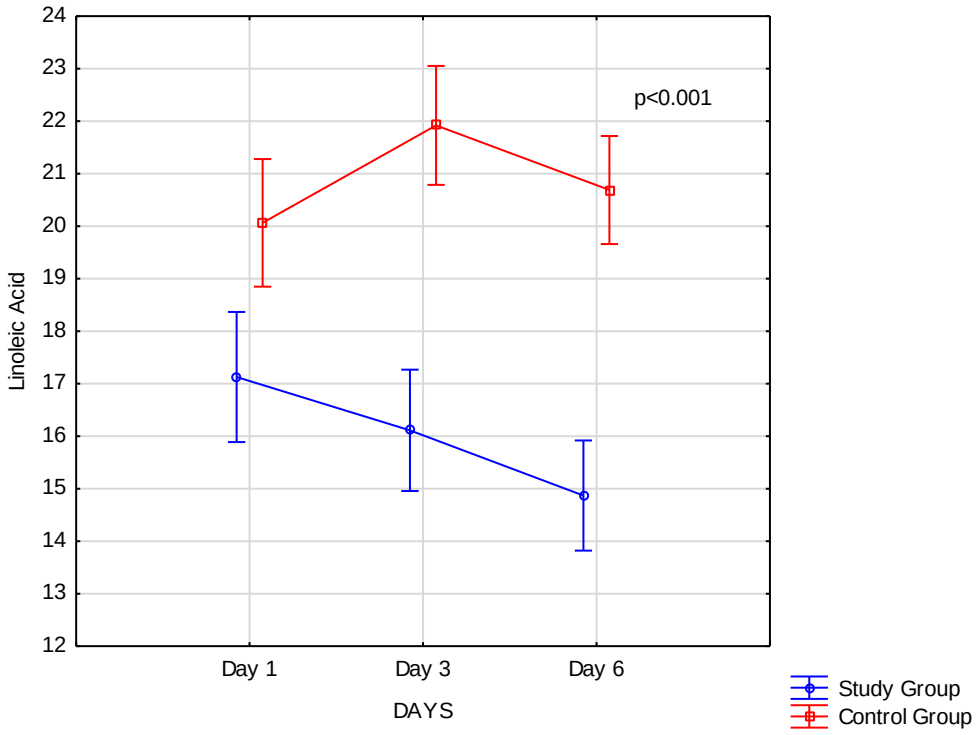

Figure 2B: Change in linoleic acid per group over the study period

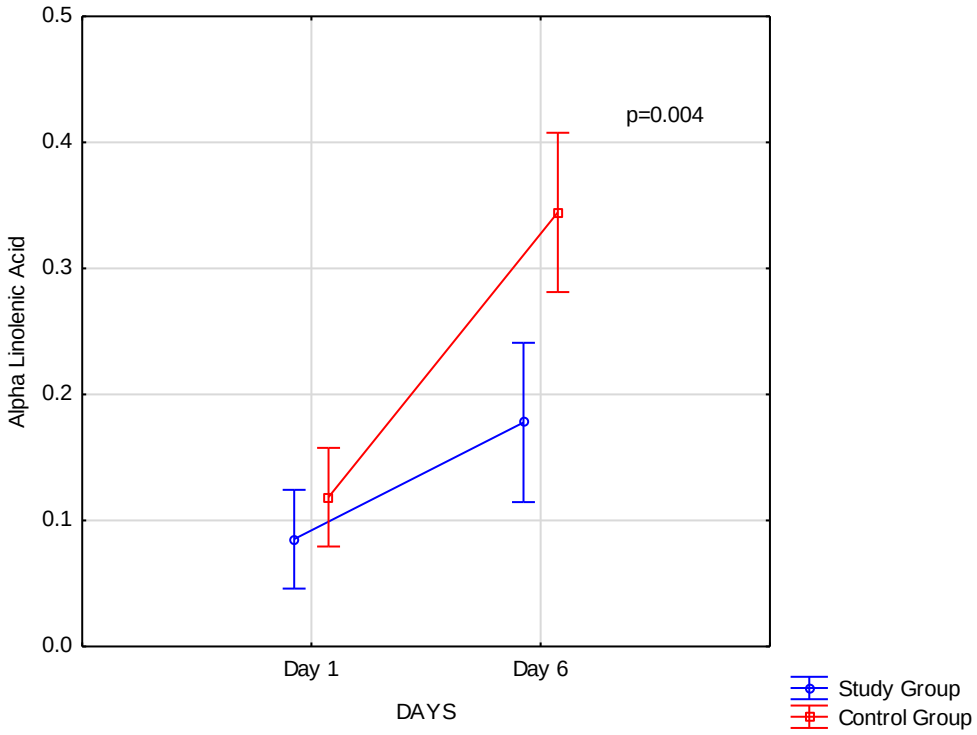

Figure 2C: Change in alpha linolenic acid per group over the study period

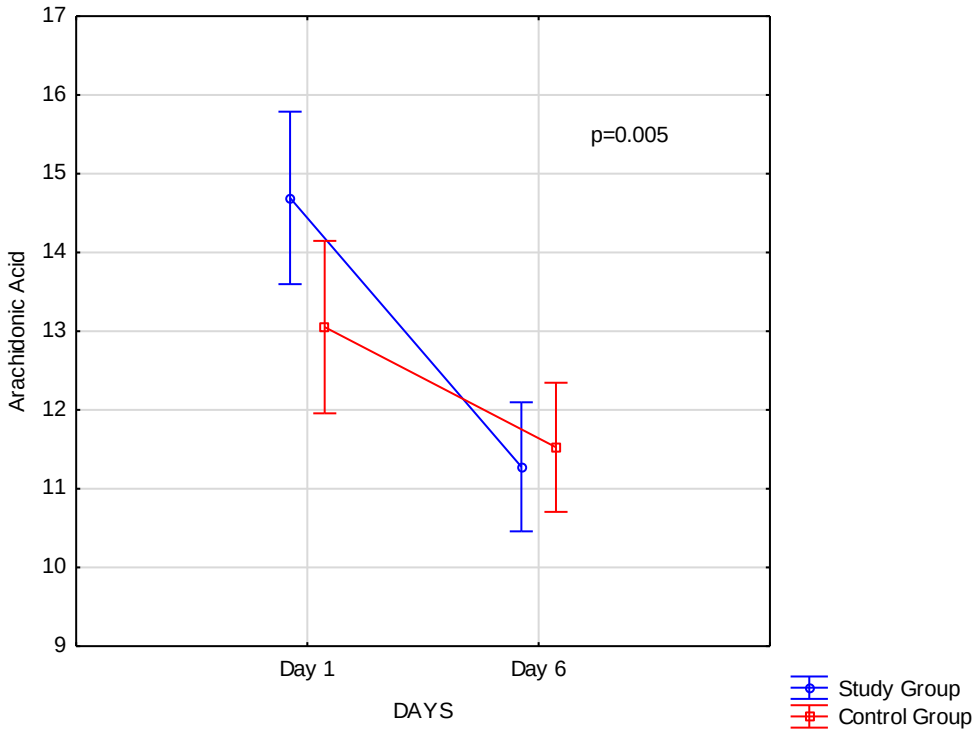

Figure 2D: Change in arachidonic acid per group over the study period

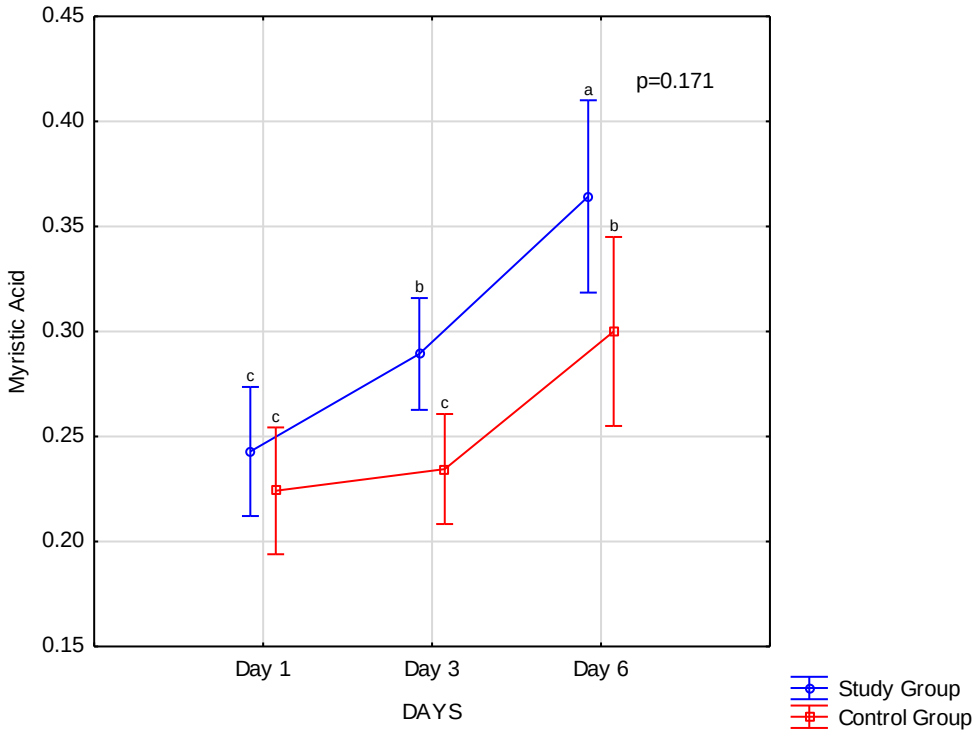

Figure 2E: Change in myristic acid per group over the study period

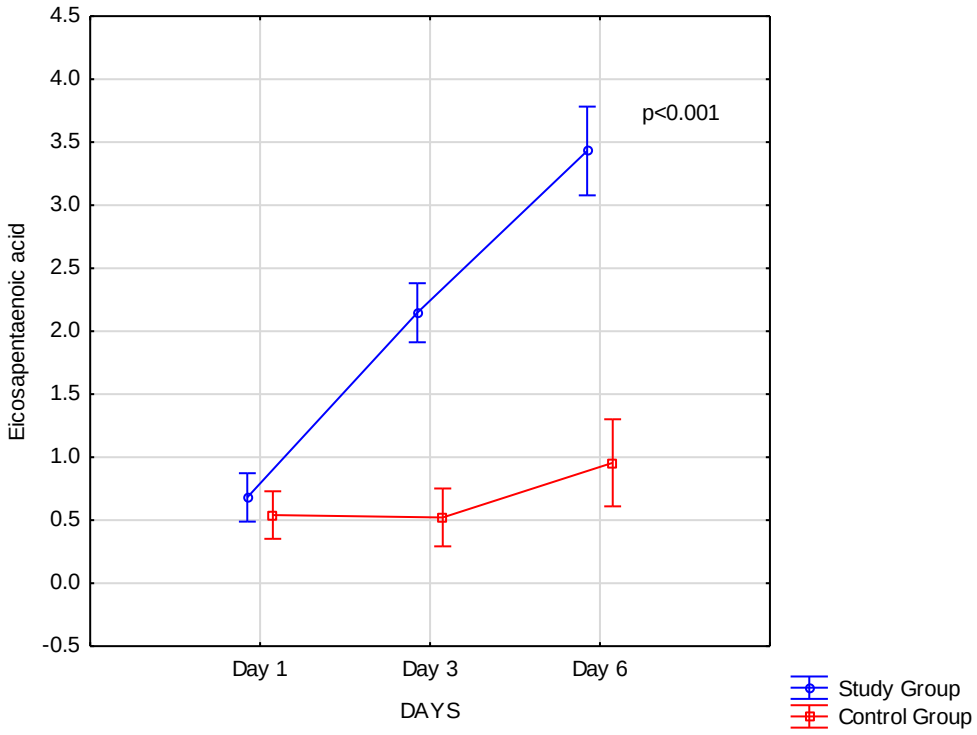

Figure 2F: Change in eicosapentaenoic acid per group over the study period

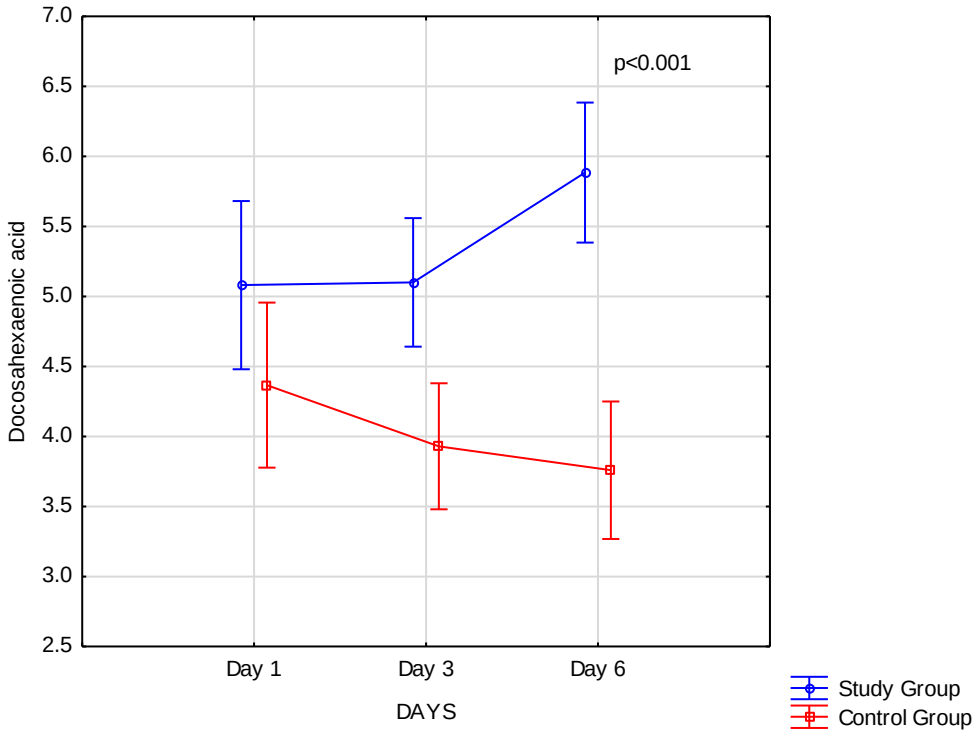

Figure 2G: Change in docosahexaenoic acid per group over the study period

Table 5: Clinical outcome measurements day 1 and day 6

	Study Group						**Control Group**						
	Day 1			**Day 6**			**Day 1**			**Day 6**			**Comparison between SG and CG**
	Mean ± SE	**-95% LCL**	**+95% UCL**	**Mean ± SE**	**-95% LCL**	**+95% UCL**	**Mean ± SE**	**-95% LCL**	**+95% UCL**	**Mean ± SE**	**-95% LCL**	**+95% UCL**	***p* value**
SOFA score	5.77 ± 0.75	4.26	7.28	4.27 ± 0.77	2.72	5.82	5.91 ± 0.86	4.191	7.635	3.83 ± 0.88	2.06	5.6	*p*=0.578
CRP (mg/L)	199.82 ± 23	153.74	245.9	103.6 ± 13.9	75.71	131.46	215.47 ± 23.4	168.56	262.37	116.99 ± 14.16	88.62	145.36	*p*=0.951

SOFA: Sequential Organ Failure Assessment; CRP: C-reactive protein; LCL: lower confidence limit; UCL: upper confidence limit

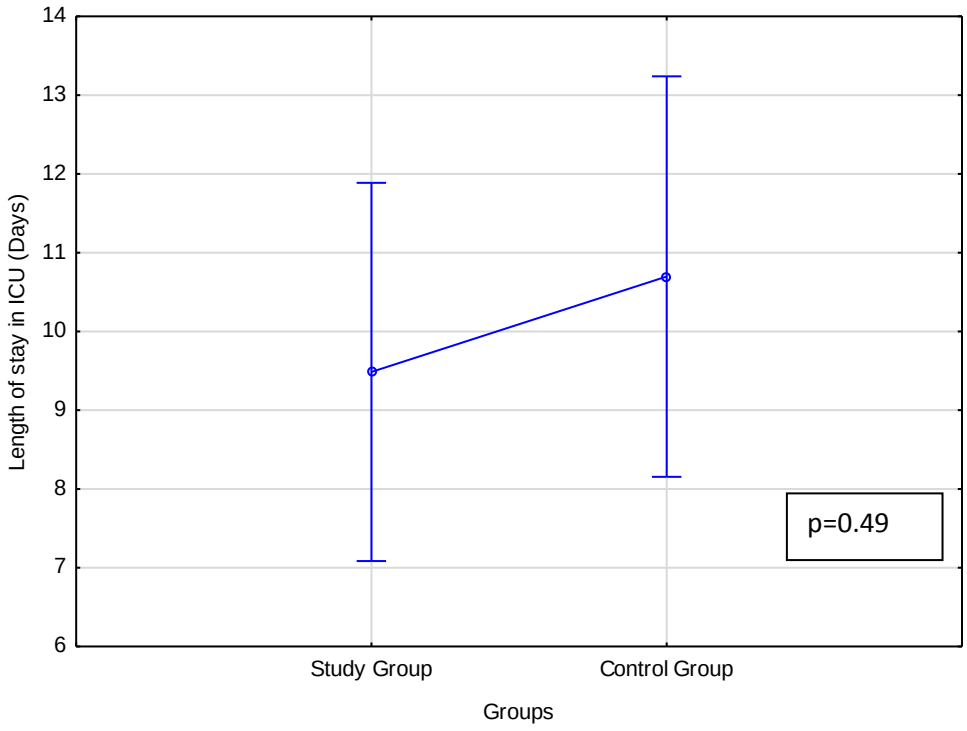

Figure 3: Length of stay in ICU

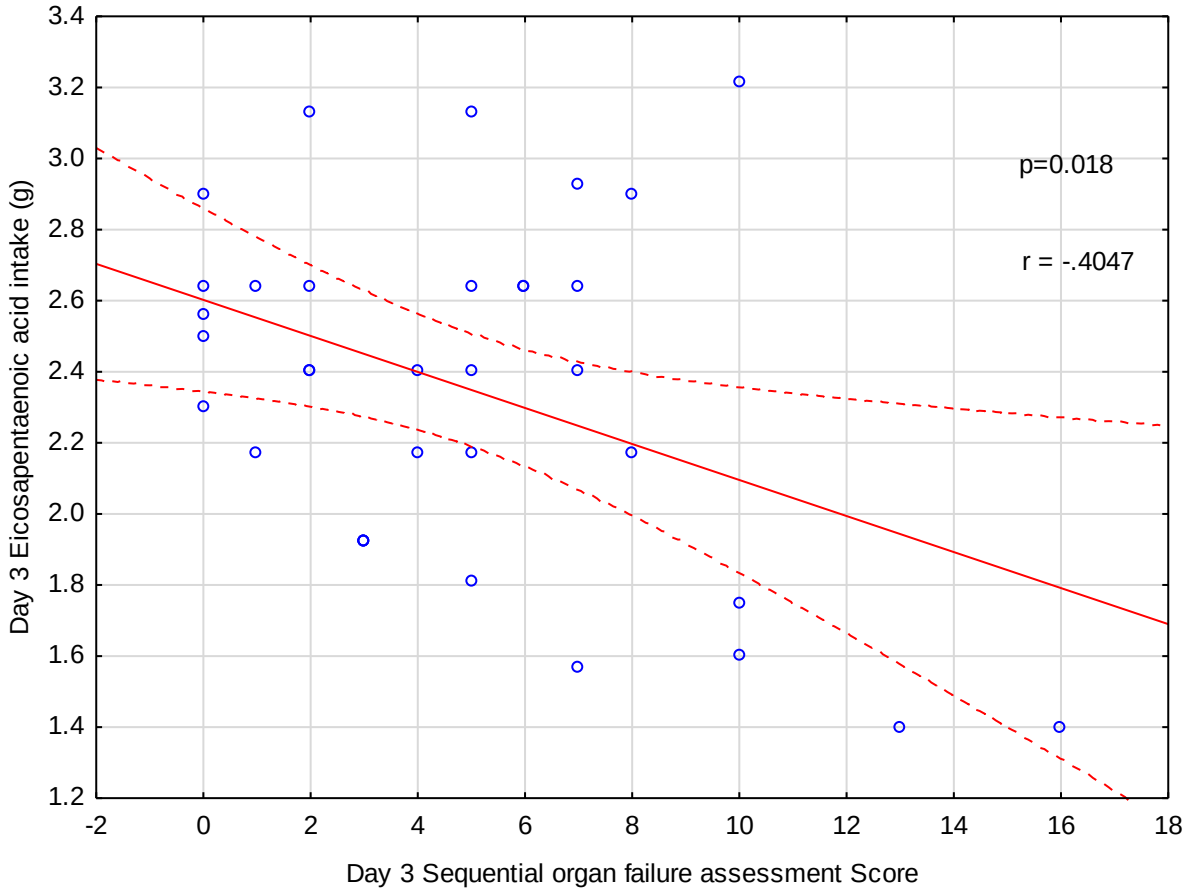

Figure 4: Correlations between day 3 eicosapentaenoic acid intake and day 3 Sequential Organ Failure Assessment Score

Discussion

This study set out to compare a 4-oil LE containing FO (SMOFlipid®) with a 100% soybean-based LE in terms of routine biochemical and physiological markers, plasma total phospholipid FA profile, organ dysfunction, and clinical outcomes in ICU patients with SIRS, with or without sepsis, or ARDS. To our knowledge this is the first randomised controlled study using SMOFlipid® in septic ICU patients, although it has been used previously in post-surgery patients (25).

In this study the baseline characteristics of the patients did not differ between the two groups. The nutritional intakes also did not differ, except on day 3 the CG received more energy per kilogram body weight and the SG received FO, providing EPA and DHA over the study period, as well as α-tocopherol. The highest intake of FO, EPA and DHA was on day 3, as EN was started on approximately day 4 in both groups. This study demonstrated a significant increase in OA and ALA in both groups. Plasma EPA showed a significant increase in the SG, whereas DHA increased after day 3. DHA levels decreased significantly in the CG. AA decreased in both groups. Similar results were seen using the same LE in surgical patients. Grimm et al. demonstrated an increase in n-3 PUFAs, EPA and DHA, and a decrease in LA, AA and total n-6 PUFAs after 6 days (25).

Similar results were seen with other FO containing LEs studied in critically ill and septic patients. In the study by Barbosa et al., the use of FO containing LE was associated with increases in plasma EPA, but showed no differences in DHA and AA concentrations (26). Mayer et al. demonstrated a marked increase in EPA and DHA concentrations in patients receiving FO-based infusions. The levels plateaued after 7 days; the sum of EPA and DHA surpassed the AA level nearly twofold (27).

Other FO containing LEs have also been used in post-surgical patients, demonstrating a significant increase in EPA and DHA levels and n-6:n-3 PUFAs ratio, but showing no difference in AA levels in both groups (28) and improved clinical outcomes (29-34).

The optimal ratio of n-6:n-3 PUFAs has been questioned and whether the provision of an LE with an optimum ratio would be associated with metabolic and clinical benefits. Based on previous studies, a ratio between 2:1 and 4:1 can be considered as beneficial to severely ill patients (14-17). SMOFlipid® was developed to have an optimal n-6:n-3 PUFAs ratio of 2.5:1. In this study, the plasma n-6:n-3 PUFAs ratio decreased significantly in the SG, whereas it remained fairly constant in the CG. The plasma ratio on day 6 in the SG was similar to the values recommended for lipid emulsions (34). Similar results were also seen in surgical patients where the ratio n-6:n-3 PUFAs was profoundly elevated and leukotriene B_5 release from n-3 PUFAs was also enhanced on day 6, whereas the release of leukotriene B_4 from n-6 PUFAs was lowered with SMOFlipid® (25).

In terms of clinical outcomes, this study showed an improvement in CRP levels in both groups and a positive correlation was shown between day 3 EPA intake and reduction in CRP levels. Days on mechanical ventilation, LOS in the ICU and mortality were not different between the two treatment groups; however the SG was associated with a shorter ICU LOS. SOFA score also improved in both groups: a significant correlation was found between day 3 EPA intake and day 3

improvement in the SOFA score. Grimm et al. demonstrated a significant reduced length of hospital stay (13.4 ± 2.0 vs 20.4 ± 10 days) (25). Heller et al. demonstrated a reduction in ICU LOS when the n-6:n-3 PUFAs ratio was 2:1 (34).

A secondary analysis of data comparing the effects of different IV fat emulsions from a prospective multicentre study showed that patients receiving soybean oil, compared with patients receiving either olive or fish oil, had a shorter time to termination of mechanical ventilation and ICU discharge alive (35). Heller et al. (36) used an FO supplement in a heterogeneous group of patients including trauma, post-surgical and septic patients, and identified a dose-dependent (0.1–0.2g/kg) reduction in mortality, infection rate and length of stay. Grecu et al. showed significant reduction in reoperation rates, ICU and hospital LOS, but no difference in mortality (37). Another study using the same FO supplement showed a significant decrease in new organ dysfunction, but no significant decrease in LOS (38). Other FO-containing LE studies reported no effect on length of stay (26, 39-41), days on mechanical ventilator (26, 27, 39, 41) and mortality (26, 27, 39-41).

A recent meta-analysis confirmed a significant reduction in infection rates by 35% in critically ill patients with no overall effect on ICU LOS. They concluded that FO admixtures and FO supplement LE are advantageous for the majority of patients compared with LCT or MCT/LCT LE because of their balancing omega-3 content (42). However, a review published recently found insufficient high-quality data investigating the true effect of PN with FO containing LEs compared with other IVLEs on clinical outcomes (43).

It is difficult to compare the results of this study with other FO studies owing to the different dose of FO and duration of treatment.

The limitations of this study are that only half the patients received PN for 6 days; this affected the duration as well as the dose of FO over the study period. There was a definite signal that the intake of EPA and FO on day 3 showed a beneficial effect. It was not possible to determine the full nutritional intake throughout the study period owing to the incomplete recording of EN intake. Infection rate, as well as days on antibiotics, was also not documented and would have provided valuable information about clinical outcomes. The study population may have been somewhat heterogenous as to the causes and severity of SIRS and ARDS. Finally, we were unable to test plasma α-tocopherol levels, which would have been an interesting additional result as the intake was significantly different between the two groups.

Conclusion

This study results suggest that PN containing a 4-oil LE with FO at a dose of 0.09 – 0.22/kg in adult ICU patients with SIRS, with or without sepsis, or ARDS, showed multiple positive changes in the plasma total phospholipid fatty acid profile. Both plasma EPA and DHA increased significantly in the SG. The n-6:n-3 PUFA ratio decreased in the SG and remained fairly constant in the CG. The 4-oil LE appears to be safe and well tolerated. There was no significant difference in terms of CRP,

SOFA, length of ICU stay and mortality. Additional studies need to be done in this patient population, paying particular attention to the dose and timing of FO, EPA and n-6:n-3 PUFA ratio per day, and their effect on clinical outcomes.

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4.3 ADDITIONAL RESULTS

Dietary data

Both groups were well matched for baseline characteristics. Nutritional intake of total energy, protein, fat and glutamine did not differ significantly between the groups throughout the study period, except on day 3 the energy provided per kilogram body weight was significantly more in the CG (p=0.041). The study group (SG) fish oil (FO) intake was significantly higher throughout the study providing between 0.09 ± 0.03g (day 1) and 0.22 ± 0.11g/kg/day (day 3) (Figure 1). The time of commencement of enteral nutrition as well as the calculation of all nutrients (including oral, enteral and parenteral) was unfortunately neither defined nor controlled in the protocol. In line with hospital protocol and guidelines, early enteral nutrition was initiated in nearly half the patients, which resulted in a reduced fish oil intake through IVLE.

The phytosterol intake was significantly more in the control group (CG) (p<0.001) (Fig. 2) throughout the study. Similarly, the alpha-tocopherol intake was significantly more in the SG (p<0.001) (Fig. 3).

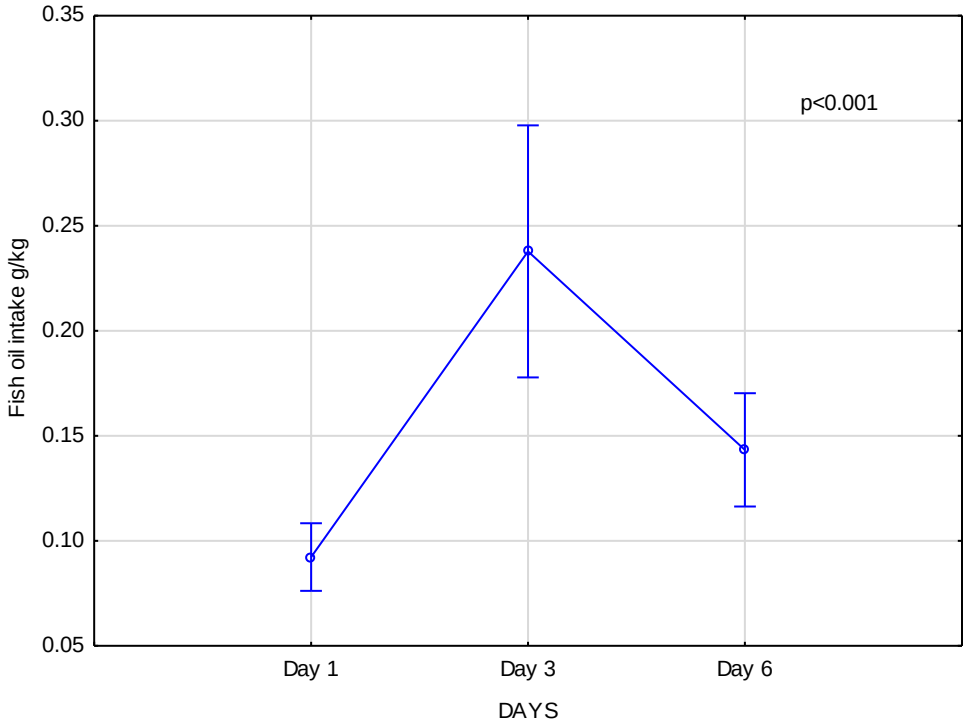

Figure 1: Fish oil intake in the study group

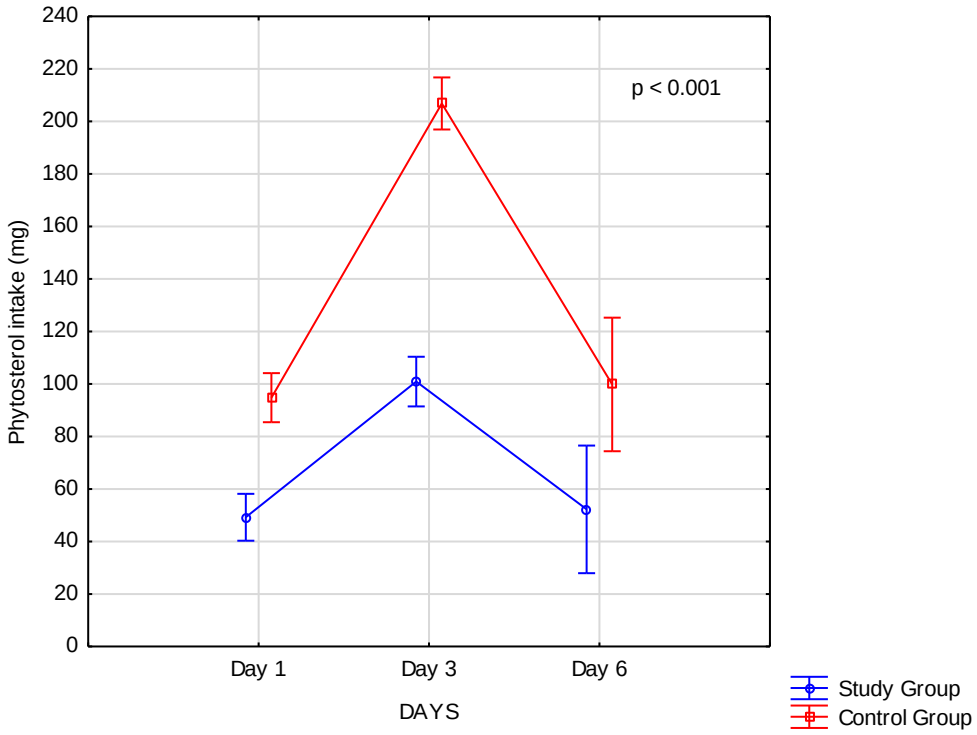

Figure 2: Phytosterol intake throughout study period

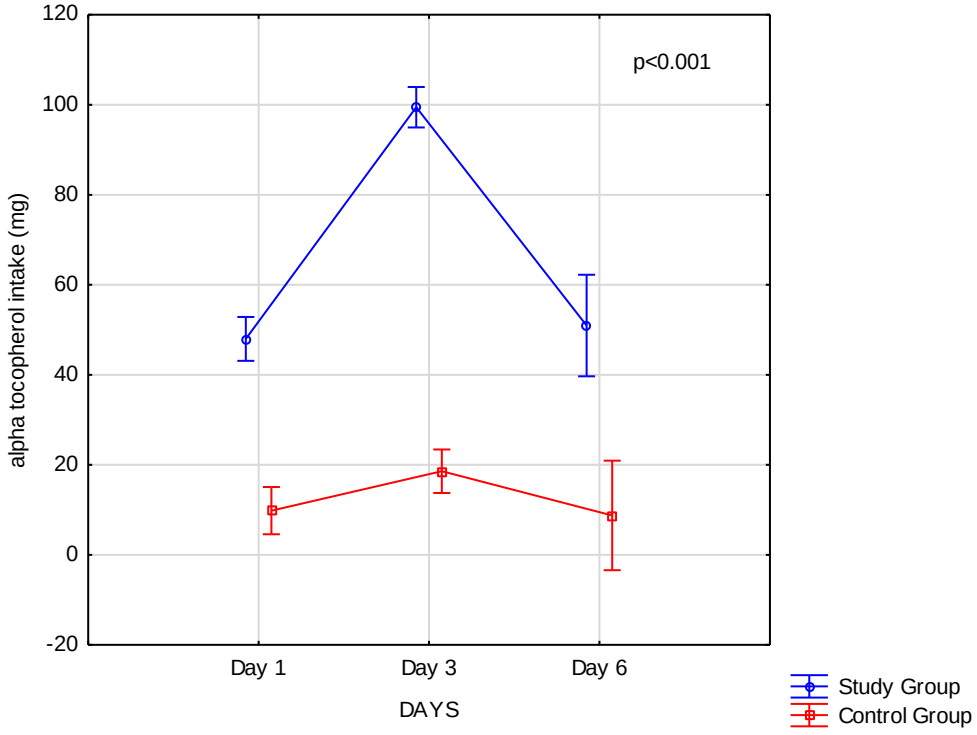

Figure 3: Alpha-tocopherol intake throughout study period

Ventilatory function

Days on mechanical ventilation did not differ between the two groups (Table 1). Both groups received steroids: the mean days on steroids were slighter longer in the SG but were not significant (p=0.775). A correlation was found between days on steroids and days on mechanical ventilation (r=0.298, p=0.012) (Fig. 4). A non-significant negative correlation was also shown for day 3 EPA intake and days on mechanical ventilation (r=-0.201, p=0.224).

Table 1: Days on mechanical ventilation

	Study Group (*n*=38)	**Control Group (*n*=33)**	***p* value**
Days on mechanical ventilation	1.658 ± 2.317	1.515 ± 1.805	p=0.775

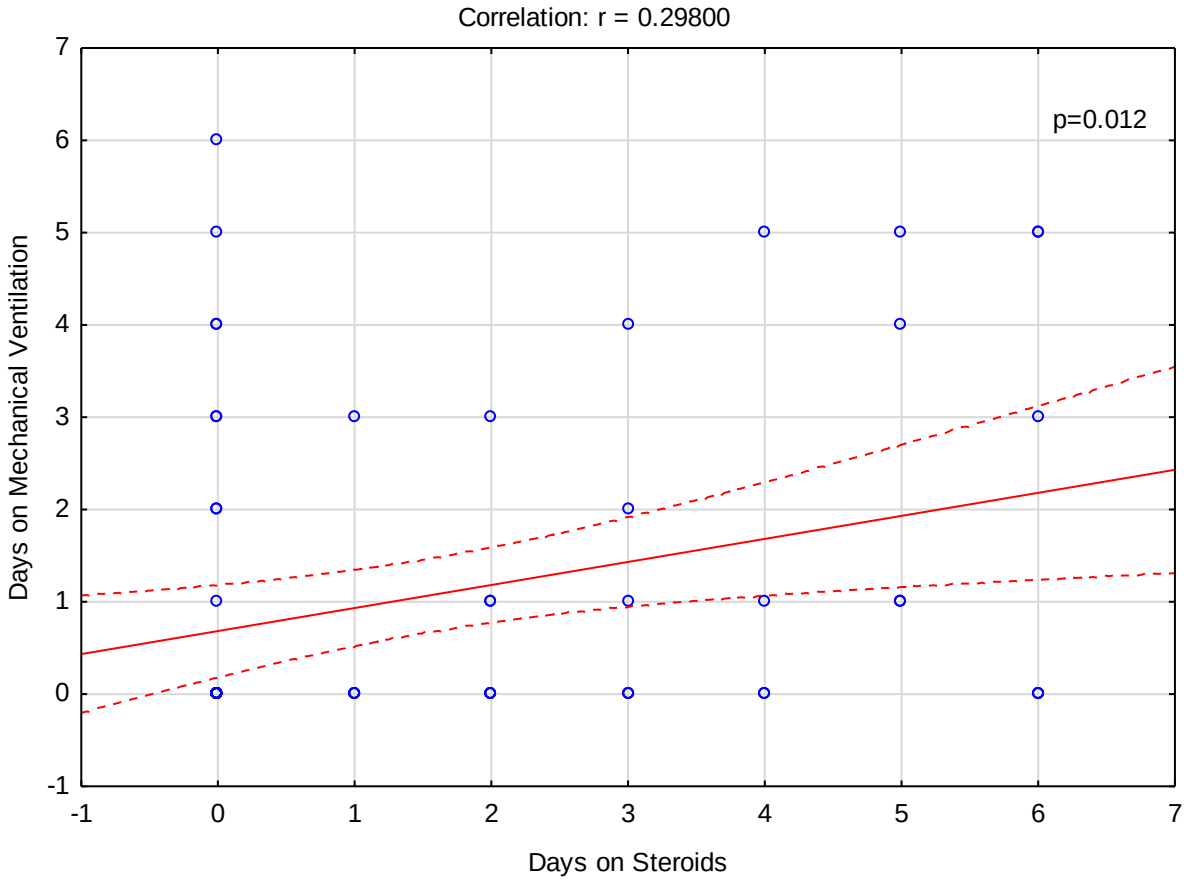

Figure 4: Correlation between days on steroids and days on mechanical ventilation

CHAPTER 5

DISCUSSION

This study set out to compare a 4-oil lipid emulsion (LE) (30% soybean oil (SO), 30% medium-chain triglycerides (MCTs), 25% olive oil (OO) and 15% fish oil (FO)) (SMOFlipid®) with a 100% soybean-based LE in terms of its effect on (i) routine biochemical and physiological parameters, (ii) gas exchange, (iii) inflammatory mediators, (iv) plasma total phospholipid fatty acid (FA) composition, and various clinical outcomes in adult intensive care unit (ICU) patients with SIRS, with or without sepsis, and acute respiratory distress syndrome (ARDS).

It was postulated that the LE containing FO would result in improved biochemical markers, i.e. less effect on plasma triglycerides and liver enzymes, improved oxygenation, reduced concentrations of pro-inflammatory cytokines, i.e. tumour necrosis alpha (TNF-α), interleukin (IL)-1 and IL-6, and increased concentrations of anti-inflammatory cytokine IL-10, improved plasma eicosapentaenoic acid (EPA) and reduced omega-6 (n-6):omega-3 (n-3) polyunsaturated FA (PUFA) ratio, and improved clinical outcomes, i.e. reduction in sequential organ failure assessment (SOFA) score, fewer days on mechanical ventilation, reduced ICU length of stay (LOS) and reduced mortality.

To our knowledge, this is the first randomised controlled study using SMOFlipid® in adult septic ICU patients, although it has been studied previously in post-surgery patients (1-8).

5.1 Patient description and baseline parameters

A total number of 75 adult patients were included in the study and randomised to receive either parenteral nutrition (PN) with a 4-oil LE (Study Group (SG)) or PN with a 100% soybean oil LE (Control Group (CG)). Seven patients were excluded, a total of 68 patients remained, and 35 patients were randomised in the SG and 33 in the CG.

A number of studies have been conducted in critically ill patients comparing the effects of intravenous (IV) FO LE with other LE. Table 5-1 compares the current study with previous studies in terms of number of study participants, duration of intervention, and baseline descriptors, namely, SOFA score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Simplified Acute Physiology Score (SAPS II), age, and body mass index (BMI). The APACHE II or SAPS II scores are used in the various studies to predict the severity of the disease and risk of short-term mortality (9). The number of study participants of this study was relatively high compared with the other studies.

Table 5-1: Comparison of study participants and baseline descriptors of the current study versus previous studies in critically ill patients

Author	Patient number	Duration of intervention	Baseline descriptors		
				Study Group	Control Group
Our study	68 SIRS and septic patients	5 days	APACHE II SOFA Age BMI	13.7 ± 7.5 5.7 ± 4 60.8 ± 13.9 29.2 ± 11	11.2 ± 8.1 5.1 ± 4.2 55.7 ± 14.8 27.6 ± 5.9
Barbosa (10)	25 sepsis patients	5 days	SOFA SAPS II Age BMI	9.5 ± 0.9 47.5 ± 5 70 ± 2 28.9 ± 1.7	8.9± 1.2 41.6 ± 6.5 57 ± 5 28.5 ± 2.6
Sungurtekin (11)	20 sepsis and 20 SIRS patients	7 days	APACHE II Age BMI	19.8 – 21.9 44.4 – 54.0 25.4 – 26.3	20.5 – 28.0 61.4 – 69.6 26.4 - 28
Friesecke (12)	116 critically ill medical patients	≥ 7 days	SAPS II Age	49 ± 18 63 ± 13	54 ± 17 66 ± 11
Hall (13)	60 sepsis patients	14 days or until discharge	APACHE II SOFA Age	19.1 ± 6.7 7.2 ± 3.0 63.8 ± 11.7	17.9 ± 6.2 7.6 ± 3.2 64.5 ± 13.4
Edmunds (14)	451 critically ill patients 19 pts in FO group	12 day or death	APACHE II Age BMI	24.3 ± 6.8 6 66.2 ± 18.3 27.4 ± 18.3	22.4 ± 7.9 63.5 ± 15.9 28.4 ± 8
Khor (15)	28 patients with severe sepsis	5 days	APACHE II Age BMI	19.3 ± 7.8 64.8 ± 17.4 21.5 ± 5.2	16.3 ± 7.2 73.8 ± 14.2 21.4 ± 5.6
Mayer (16)	21 septic patients	5 days	N/A	N/A	N/A
Mayer (17)	10 septic patients	10 days	APACHE II	14 - 34	9 - 23
Heller (18)	661 ICU patients	≥ 3 days FO at different doses	SAPS II Age BMI	32.2 ± 13.6 62.8 ± 16.5 25.1 ± 4.2	
Grecu (19)	54 patients with abdominal sepsis	5 days	N/A	N/A	N/A
Grau-Carmona (20)	159 critically ill patients	5 days	APACHE II SOFA Age BMI	21 ± 5 6.8 ± 3.6 60.7 ± 17.3 26.6 ± 4	21 ± 6 7 ± 3.3 60.6 ± 16.4 27.1 ± 4
Wang (21)	40 patients with acute pancreatitis	5 days	APACHE II SOFA Age BMI	12 ± 3 6 ± 0.8 40 ± 10 22.3 ± 1.2	13 ± 4 7 ± 1.1 37 ± 9 21.8 ± 2.1

Abbreviations: SOFA: Sequential Organ Failure Assessment; SAPS II: Simplified Acute Physiology Score; APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: body mass index measured as kg/m^2; Age: measured in years; N/A: not available in article.

The majority of the participants were surgical admissions with an average age of 61 years in the SG and 56 years in the CG. The ages were similar to those of the study participants in Grau-Carmona et al. (Table 5-1), Ma et al. and Allingstrup et al., where the average ages ranged from 61.55 to 62.9 years and 58.8 to 60.3 years respectively (20, 22, 23).

The average body mass index (BMI) in this study was 29 kg/m^2 in the SG and 28 kg/m^2 in the CG. The study conducted by Veldsman et al. in another South African ICU showed similar results, with a mean BMI of 28.5 ± 8.1 kg/m^2 (24). The mean APACHE II score was 14 (SG) and 11 (CG), which was similar to Wang et al., but lower than other studies on critically ill patients (21). These values are reported in Table 5-1 (11, 13-16, 20, 21) and the average SOFA score on admission was 5.7 in the SG and 5 in the CG, which was also lower than the other studies performed in critically ill patients (see Table 5-1 for SOFA scores from other studies) (10, 13, 20, 21).

The baseline characteristics of the patients did not differ between the two treatment groups with regard to age, BMI, APACHE II and SOFA scores, temperature, heart rate, biochemical parameters, including triglycerides and liver functions, PaO_2/FiO_2 ratio, and cytokine levels.

The nutritional intake in terms of total energy, carbohydrates, protein, lipids, glutamine and micronutrients also did not differ, except the CG had a higher energy per kilogram body weight intake on day 3 and the SG received FO (0.09g/kg minimum to 0.22g/kg maximum), providing EPA, DHA and higher levels of α-tocopherol over the study period. The highest intake of FO, EPA and DHA was on day 3, as enteral nutrition (EN) was started on approximately day 4 in both groups. The cumulative FO intake was statistically significant in the SG between the patients that received PN for 6 days compared with those who did not (p=0.032). The intake of phytosterol was significantly less in the SG. There is evidence that large intakes of phytosterols can cause cholestasis and PN-associated liver disease (PNALD) (25). A study conducted in adult patients on home PN showed a correlation between total plasma phytosterol levels, liver function tests and platelet counts. A strong correlation was shown between total plasma phytosterol levels, total bilirubin levels and AST levels and a weaker correlation for platelet counts (26). A study conducted by Ellegård et al. concluded that adult patients with short-bowel syndrome (SBS) receiving PN had higher serum levels of phytosterols compared with other SBS patients not receiving PN, possibly owing to the phytosterol content in LE (27). PNALD has also been studied in the paediatric population. Savini et al. measured plasma phytosterol concentrations in preterm infants receiving five different LEs. The participants receiving the 100% soybean oil LE had significantly higher plasma phytosterol concentrations (28). Clayton et al. reported a link between plasma phytosterol concentrations and cholestatic liver disease in 29 children (29). Although these two studies were conducted in children, the concept of PN and the LE content contributing to the phytosterol levels remains the same.

5.2 Biochemical and physiological markers

Biochemical and physiological markers were measured at baseline (day 1), day 3 and day 6. Throughout the study comparisons were made between the two treatment groups, as well as within each group to detect differences between baseline and day 6 measurements.

There were no statistically significant differences between the groups with regard to WCC, blood glucose, triglycerides (TGs), liver enzymes and total bilirubin throughout the study period. Looking at within-group changes over time, however, showed a significant increase for triglyceride levels from day 1 to day 6, in both groups; however the range was wider in the CG. LEs containing only long-chain triglycerides (LCTs) and those containing 50% long-chain triglycerides and 50% medium-chain triglycerides (LCTs/MCTs) have been shown to increase plasma TG levels (1, 6, 11, 30), whereas FOs containing LEs have shown a significant reduction in plasma TG levels in surgical patients or maintaining the levels within normal ranges (1, 4-6, 23, 30, 31). 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 with PN without FO (32). However, the meta-analysis conducted by Tian et al. found significant differences between a 4-oil LE containing SO/MCT/OO/FO vs LCT and vs OO/LCT, suggesting the beneficial effect of FO containing LE in surgical patients (33).

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. In this study, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin levels decreased in both treatment groups. AST levels decreased from day 1 to day 3 but then increased again after day 3, whereas ALT levels decreased throughout the study period in the CG. The ALT levels decreased and the gamma-glutamyl transferase (GGT) levels increased in both groups. Bilirubin levels decreased in both groups between day 1 and day 3 and then continued to decrease in the SG, but levels increased significantly in the CG after day 3 (p=0.039). A weak, negative correlation was found between day 3 EPA intake and bilirubin levels. These results are similar to findings from other studies in surgical patients, comparing FO containing LE to other LE, showing a decrease in ALT (1, 3, 5, 30,34), AST (5, 30, 34) and bilirubin (3, 30, 35), and an increase in GGT (1, 3). Some studies showed no difference in liver function test with FO LE (4, 6-8, 36). Sungurtekin et al. demonstrated an increase in liver steatosis on day 7 and 10 in patients with sepsis and SIRS on PN without FO (11). A retrospective study conducted in adult patients receiving FO supplementation in PN, showed GGT, alkaline phosphatase (ALP) and ALT decrease with FO PN supplementation. The decrease was greater when the doses of FO were higher (0.71g FO/kg – 5.28g FO/kg) (37). 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 (34, 38). Reduction in liver enzymes and improved antioxidant status with FO containing LE was also shown in four meta-analyses (32, 33, 39, 40).

Klek et al. (41) performed a study to evaluate the safety and efficacy of a 4-oil (SO/MCT/OO/FO) LE vs an LCT LE 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.

5.3 Gas exchange

This study did not demonstrate a statistical difference between the PaO_2/FiO_2 ratio between the two treatment groups on day 1 or day 6. This could be because the optimal dose of FO was only received for 2 days. Barbosa et al. showed a significantly higher PaO_2/FiO_2 ratio in the FO group compared with the MCT/LCT group, and the proportion of patients with PaO_2/FiO_2 ratio > 300 was significantly higher on Day 6 (10). Wang et al. showed a significantly better oxygenation index with n-3 PUFA supplemented PN at doses of 0.15 – 0.2g/kg/day (21). A positive non-significant correlation was found between the intake of EPA on day 3 and the improvement in PaO_2/FiO_2 ratio in the SG.

5.4 Inflammatory markers

Pro-inflammatory cytokines, namely, TNF-α, IL-1β and IL-6 and the anti-inflammatory cytokine IL-10 were measured as well as C-reactive protein (CRP). Plasma cytokine concentrations did not differ statistically between the two groups prior to initiation of PN and throughout the study period. Concentrations of TNF-α decreased from day 1 to day 6 in the SG, whereas they increased in the CG, but the changes were not significant. Concentrations of IL-1β and IL-6 decreased in the SG during the intervention and increased in the CG after day 3; however the difference was not significant. IL-10 concentrations decreased in both groups between day 1 and day 3, but then increased from day 3 to day 6 in the SG. A positive correlation was shown between the FO intake and the concentrations of IL-10.

Metry et al. demonstrated a significant reduction in IL-6 in postoperative ICU patients when comparing SMOFlipid® with LCT (8). Another study in surgical patients comparing an FO supplement and LCT versus LCT showed a significant decrease in IL-6, TNF-α and IL-1 in the FO group (36), while comparing the same LE in patients with acute pancreatitis showed a reduction of IL-6 in the FO-supplemented group at a dose of 0.15 – 0.2g/kg/day FO (226). Other studies in surgical patients comparing FO supplement plus MCT/LCT versus MCT/LCT showed a significant reduction in IL-6, TNF-α and IL-1 (30) and IL-6 and TNF-α, but no difference in IL-1 and IL-10 (35). Ma et al. compared MCT/LCT/FO LE with MCT/LCT and showed no significant difference in IL-6 and TNF-α levels (23). Wu et al. compared SO/MCT/OO/FO with MCT/LCT and reported no difference in IL-6, TNF-α and IL-10 levels (6).

Other FO containing LEs have also been studied in critically ill and septic patients. Mayer et al. demonstrated an increase in TNF-α, IL-1 and IL-6 in the LCT group (high in omega-6 polyunsaturated fatty acid (PUFA)) (16). Sungurtekin et al. demonstrated an increase in IL-6 and TNF-α on day 7 and an increase in IL-1 on day 3, 7 and 10 in septic patients receiving MCT/LCT LE.

They also showed an increase in IL-10 in the group receiving FO LE at the dose of 0.6g/kg/day (11). Barbosa et al. showed a reduction in IL-6 and a lesser decrease in IL-10 in the MCT/LCT/FO group compared with MCT/LCT (10). However, other studies showed no effect on IL-6 levels (12) and TNF-α levels (15).

This study showed an improvement in CRP levels in both groups as expected and a positive correlation was shown between day 3 EPA intake and reduction in CRP levels. Antebi et al. compared the same two LEs used in this study in surgical patients and demonstrated a reduction in CRP levels in the FO group (1). A reduction in CRP was also demonstrated in patients with acute pancreatitis receiving an FO supplement and LCT compared with LCT (21). However, other studies in surgical patients reported no difference in CRP levels (35, 42). Two studies in critically ill patients also reported a reduction in CRP levels in the patients receiving FO containing LE (13, 19).

5.5 Total phospholipid fatty acid profile

This study compared a 4-oil LE (30% SO, 30% MCT, 25% OO and 15% FO) (SMOFlipid®) with a 100% soybean-based LE. SO LEs are LCTs that are high in n-6 PUFA and contain high amounts of linoleic acid (LA) and moderate amounts of α-linolenic acid (ALA). MCTs are short-chain FAs and include caprylic, caproic and myristic acids. OO is rich in omega-9 FA and contains oleic acid (OA) and small amounts of LA, and FO LEs are high in n-3 PUFA and contain EPA and DHA (43).

This study demonstrated a significant increase in OA and ALA in both groups. Plasma myristic acid increased in the SG throughout the study period and only increased between day 3 and day 6 in the CG. Plasma concentrations of myristic acid were significantly different on day 3 between the SG and the CG. Plasma EPA showed a significant increase in the SG, whereas DHA increased slightly only on day 6. DHA levels decreased significantly in the CG throughout. Arachidonic acid (AA) decreased in both groups. Similar results have also been shown in critically ill patients, in the study by Barbosa et al. who compared an LE containing MCT/LCT/FO with an LE with MCT/LCT. The FO containing LE was associated with a significant increase in plasma EPA, but showed no differences in DHA and AA concentrations between the two groups (10). Mayer et al. demonstrated a marked increase in EPA and DHA concentrations and a decrease in AA levels in septic patients receiving FO-based infusions and LCT compared with LCT. The FA profile remained unchanged in the LCT group (16, 17).

In surgical patients, Grimm et al. compared an LCT/MCT/OO/FO LE with LCT and demonstrated an increase in n-3 PUFA, EPA and DHA, and a decrease in LA, AA and total n-6 PUFA after 6 days (2). Klek et al. (41) also showed a positive change in the fatty acid profile in intestinal failure patients on long-term parenteral nutrition receiving the same LE.

Other FO containing LEs have also been used in post-surgical patients, demonstrating a significant increase in EPA and DHA levels (31, 44) or just EPA levels (21,45), and showing a decrease in AA levels in both groups and no difference between the groups (44, 45).

The optimal ratio of n-6:n-3 PUFA has been questioned and whether the provision of an LE with an optimum ratio would be associated with metabolic and clinical benefits. Based on previous studies, an n-6:n-3 PUFA ratio between 2:1 and 4:1 can be considered as beneficial to severely ill patients (25,46-48). SMOFlipid® was developed to have an optimal n-6:n-3 PUFA ratio of 2.5:1. In this study, the plasma n-6:n-3 PUFA ratio decreased significantly in the SG (from 5.61:1 to 2.84:1), whereas it remained fairly constant in the CG. Similar results were shown by Mayer et al. in septic patients where the ratio n-6:n-3 PUFA decreased to 2.5:1 after 3 days on an FO LE (17). A decrease in n-6:n-3 PUFA in surgical patients has also been demonstrated by Grimm et al., comparing the same two LEs used in this study (2). Various other studies in surgical patients using other FO containing LEs have also demonstrated a reduction in n-6:n-3 PUFA ratio (35, 44, 45, 49). Leukotriene B_5 (LTB_5) is generated from n-3 PUFAs and leukotriene B_4 (LTB_4) is generated from n-6 PUFAs. These have also been studied in surgical patients by Grimm et al., showing an increased release of LTB_5 and a decreased release of LTB_4 on day 6 with LCT/MCT/OO/FO LE (2). Similar results have also been demonstrated with other FO containing LEs in critically ill (17) and surgical patients (35, 45).

5.6 Clinical outcomes

In terms of clinical outcomes, days on mechanical ventilation (MV), ICU LOS and mortality were not different between the two treatment groups; however the SG had a shorter ICU LOS. The SOFA score also improved in both groups, a medium and significant correlation was found between day 3 EPA intake and day 3 improvement in the SOFA score. Grimm demonstrated a significant reduced length of hospital stay (13.4 ± 2.0 days in FO group versus 20.4 ± 10 days in LCT group) comparing the same two LEs (2). Heller demonstrated a reduction in ICU LOS when the n-6:n-3 PUFA was 2:1 (18).

Other FO containing LEs studied in critically ill patients showed a significant reduction in nosocomial infections and prolonged predicted time free of infection; however the shorter length of mechanical ventilation and hospital stay in the FO group was not significant (20). Other studies demonstrated significant reduction in re-operation rates, ICU and hospital LOS (19), less new organ dysfunction (13), and reduced infection rate and antibiotic usage (18).

Studies conducted in surgical patients receiving FO LEs have shown a reduction in infections (30, 42, 50, 51), fewer days on mechanical ventilation (52) and reduction in hospital length of stay (45, 50, 51). Berger et al. and Han et al. showed a non-significant trend to reduction in ICU and hospital length of stay (30, 31). A secondary analysis of data comparing the effects of different IV fat emulsions from a prospective multicentre study showed that patients receiving either olive or fish

oil compared to those receiving soybean oil had a shorter time to termination of mechanical ventilation and ICU discharge alive (14).

Heller et al. (53) used an FO supplement in a heterogeneous group of patients, including trauma, post-surgical and septic patients, and identified a dose-dependent (0.1–0.2g/kg) reduction in mortality, infection rate and length of stay.

A recent meta-analysis confirmed a significant reduction in infection rates by 35% in critically ill patients with no overall effect on ICU LOS, but found no clear-cut effect on TNF-α levels (54).

There are a few studies in critically ill patients using FO containing LEs showing no effect on clinical outcomes, namely, effect on length of stay (10, 12, 15,16), days on mechanical ventilation (10, 12, 17) and mortality (10, 12, 15-17, 19). In surgical patients, a few studies also showed no effect on mortality using FO containing LEs (30, 45, 49,50).

The dose of fish oil administered in this study was 0.09 – 0.22g/kg and is consistent with the dose that other studies have found to be clinically favourable 13, 20, 37, 53). The highest dose of FO was on day 3 as EN was started afterwards and resulted in a reduction in PN intake and FO intake. The dosage of FO that showed benefit was 0.1 – 0.15g/kg/day (39) and 0.07 – 0.225g/kg/day (32).

5.7 Safety

Adverse reactions did not differ between the treatment groups and no serious or unexpected adverse events were reported, confirming the findings of a variety of clinical trials that PN containing FO is safe in critically ill patients (10, 13, 20, 49, 53, 55).

5.8 Hypothesis statements

This study supports the hypothesis that a FO containing IV LE compared with a soybean oil IV LE results in less inflammation (reduction in TNF-α levels) and increased plasma EPA levels. However, we could not prove a difference in gas exchange and clinical outcomes. Additional studies need to be conducted in the area of gas exchange and improved clinical outcomes, paying particular attention to the dose and duration of FO LE intake to prove this hypothesis.

The hypothesis that FO containing IV LE results in less inflammation and increased plasma EPA levels is accepted. However, the hypothesis that FO containing IV LEs improves gas exchange (PaO_2/FiO_2 ratio) and clinical outcomes (days on mechanical ventilation, length of ICU stay and mortality) is rejected.

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CHAPTER 6

CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

This study set out to determine the effects of a 4-oil lipid emulsion (LE) (30% soybean oil (SO), 30% medium-chain triglycerides (MCTs), 25% olive oil (OO) and 15% fish oil (FO)) (SMOFlipid®) compared with a 100% soybean-based LE on routine biochemical and physiological parameters, gas exchange, inflammatory mediators, plasma total phospholipid fatty acid (FA) composition, and clinical outcomes in adult Intensive care unit (ICU) patients with the systemic inflammatory response syndrome (SIRS), with or without sepsis, or the acute respiratory distress syndrome (ARDS).

It was hypothesised that the 4-oil LE would improve biochemical markers, improve oxygenation, reduce pro-inflammatory cytokines and increase anti-inflammatory cytokine IL-10, improve plasma eicosapentaenoic acid (EPA) and reduced the omega-6 (n-6):omega-3 (n-3) polyunsaturated FA (PUFA) ratio, and improve clinical outcomes.

The results suggest that PN containing a 4-oil LE with FO (Study Group (SG)) at a dose of 0.09 – 0.22g FO/kg, compared with a 100% soybean oil LE (Control Group (CG)), had a tendency to reduce liver enzymes, particularly alanine aminotransferase (ALT) and bilirubin. ALT levels decreased in both groups. Bilirubin levels decreased in both groups between day 1 and day 3 and continued to decrease in the SG until day 6, but increased significantly in the CG after day 3. Triglyceride levels were similar between the two groups.

In the SG, concentrations of TNF-α, IL-1β and IL-6 decreased from day 1 to day 6, whereas TNF-α increased in the CG, IL-1β and IL-6 also increased in the CG after day 3; however the difference was not significant. IL-10 concentrations decreased in both groups between day 1 and day 3, but then increased from day 3 to day 6 in the SG.

The SG also showed multiple positive changes in the plasma total phospholipid fatty acid profile, namely an increase in oleic acid, linoleic acid, alpha-linolenic acid, myristic acid and a decrease in arachidonic acid. Plasma EPA levels increased significantly in the SG, whereas docosahexaenoic acid (DHA) increased slightly only after day 3. The n-6:n-3 PUFA ratio decreased in the SG and remained fairly constant in the control group (CG).

No difference in PaO_2/FiO_2 ratio was shown between the two groups throughout the study period and the number of days on mechanical ventilation was no different.

Even though the mean APACHE II score was higher in the SG, there was no difference in mortality. As expected there was a reduction in C-reactive protein (CRP) and Sequential Organ Failure Assessment (SOFA) score. The ICU length of stay (LOS) was also reduced; even though it wasn't statistically significant, it could be clinically relevant.

A weak correlation was found between day 3 EPA intake and bilirubin levels, fewer days on mechanical ventilation and a reduction in CRP levels, and a significant correlation was found for improvement in SOFA score. A weak correlation was also seen between day 6 FO intake and LOS.

Additional studies need to be done in this patient population, paying particular attention to the dose and timing of FO, EPA and n-6:n-3 PUFA ratio per day and their effect on clinical outcomes.

In summary, this study showed that the administration of a 4-oil IVLE containing FO resulted in a significant increase in plasma EPA levels and n-6:n-3 PUFA ratio and a non-significant reduction in plasma TNF-α, liver enzymes (ALT and bilirubin), SOFA score and ICU LOS.

6.2 Strengths and limitations

As far as can be reasonable ascertained, this is the first randomised controlled study using SMOFlipid® in adult patients with SIRS, with or without sepsis, although it has been studied previously in post-surgery patients. The number of patients included in this study was relatively large compared with other trials in critically ill patients. The protocol of this study did not interfere with the standard of practice and ICU protocol. Although this transpired to be one of the limitations of the study in terms of the dose of FO administered over the entire study period, it is still believed to be a strength.

The limitations of this study are as follows:

Only half the patients received full parenteral nutrition (PN) for 6 days; this affected the duration as well as the dose of fish oil (FO) over the study period. There was a definite signal that the intake of EPA and FO on day 3 showed a beneficial effect.

It was not possible to determine the full nutritional intake throughout the study period owing to the incomplete recording of enteral nutrition intake.

Infection rate as well as days on antibiotics was also not documented and would have provided valuable information about clinical outcomes.

The study population may have been somewhat heterogenous as to the causes and severity of SIRS and ARDS.

Finally we were unable to test plasma α-tocopherol levels, which would have been an interesting additional result as the intake was significantly different between the two groups.

6.3 Recommendations

A similar study needs to be conducted where all nutritional intake (oral, enteral and parenteral) is documented and calculated to ensure that the patients are optimally fed throughout the study period.

Commencing enteral nutrition as soon as possible in the intensive care unit is recommended by all the guidelines and thus a recommendation would be to include enteral nutrition in the study with

high doses of FO, similar to those in the parenteral nutrition, or adding an intravenous FO supplement, thereby guaranteeing the FO intake at an optimal dose throughout the study.

Additional documentation or reporting on new infections and number of days on antibiotics would also be a useful measurement in terms of determining clinical outcomes as well as following up the patients for 28 days or until hospital discharge instead of just examining ICU length of stay.

Lastly, adequately powered, randomised controlled clinical trials assessing the impact of nutrition therapy containing intravenous FO at the dose of ≥0.2g/kg FO for a minimum of 5 days in patients with SIRS with or without sepsis are recommended.

Appendix A
Data collection protocol

MULTI- & SURGICAL ICUs AT UNIVERSITAS, PELONOMI AND WDGMC

CLINICAL NUTRITION RESEARCH

STANDARDIZED DATA COLLECTION PROTOCOL

1. General information:

Research project title:	**To investigate the effect of a fish oil containing parenteral lipid emulsion on inflammatory markers, gas exchange and clinical outcomes in septic patients.**
Researcher:	Veronique Donoghue
Study leaders:	Dr Maryke Spruyt Prof R Blaauw Dr Gunter Schleicher
Contact details	Veronique Donoghue c: +27833864001 w: (011) 5450040 Veronique.donoghue@fresenius-kabi.com
Research Assistant & Contact details:	

2. Scoring Systems

1. You will use the various scoring systems when assessing the patient.
2. The APACHE II score needs to be documented when the patient is entered into the study. (Table 1, Appendix 1). This is a point based score assessing 12 routine physiological measurements.
3. You will assess the SOFA score(Table 2, Appendix 1) on admission into the study .
4. You will also record the SOFA score daily on the case report form.
5. Renal function will be assessed using the RIFLE classification (Table 3, Appendix 1) on admission to the study and throughout the study period.
6. The RIFLE classification will be recorded on the case report form as follows:

   R: for renal risk according to the definition

   I: for renal injury

   F: for renal failure

   L: for renal loss, and

   E: for End stage kidney disease

3. Screening

1. You will consecutively enrol patients in the study. Beginning on the first day of data collection, record all patients discharged from ICU or who demised on or after that day in the screening log (Appendix II).
2. Screening log columns represent eligibility criteria for purposes of data collection. Place a ✓ in each column where a patient meets the eligibility criteria, or an ✗ if the patient does not meet that criteria. A research number should be allocated to each eligible patient and recorded on the screening log. Research numbers should be allocated consecutively from R1 to R72 as patients are entered into the study. Collect data on all patients who meet all eligibility criteria. If charts are missing and you are unable to collect all relevant data for a patient, please exclude this patient and include the next eligible patient. Screening should be continued until 72 consecutive eligible patients have been reached.

Note: Consecutive means the very next patient that meets the criteria, instead of picking and choosing patients.

3. Use additional pages of the screening log as necessary.
4. Record each patient's hospital number on the screening log.
5. Each eligible patient's research number (e.g. R1) will be recorded on the screening log.
6. Please keep the screening log to help track down which patient corresponds to which research number in case there are data queries at a later date.

Enrol all patients meeting the following eligibility criteria:

Inclusion	Exclusion
• Adults (≥ 18 years of age) • Was admitted to the ICU of Universitas, Pelonomi, WDGMC and CHBAH • Was diagnosed with Sepsis (defined as suspected or proven infection plus SIRS, the presence of two or more of the following: • Temperature >38°C or <36°C, • Heart rate >90 bpm, • Respiratory rate > 20 bpm or $PaCO_2$ <32 mmHg, and/or • White Blood count >12 000/mm^3, <4000/mm^3) • ARDS according to Berlin Definition (See Scoring Systems Table 4)Predicted to need Parenteral Nutrition for more than 5 days.	• Patients < 18 years of age • On full Enteral Nutrition. • Pregnancy • Treatment with immunosuppressive drugs • Treatments with hydrocortisone > 300mg/day at admission. • Plasma Triglycerides >400mg/dl • Cirrhotic liver and/or acute hepatitis • Chronic renal failure and/or end stage renal disease (according to the RIFLE classification). • Recent stroke • Known allergic reaction to fish or egg proteins confirmed by previous medical history.

4. Case Report Forms

- A case report form (CRF) (Appendix III) must be completed for each study participant.
- All data requested in the CRF is to be taken retrospectively from the original source documents, i.e. the patient's ICU chart/s or hospital file.
- Collect data retrospectively from the day of ICU admission until day 6 of ICU stay, discontinuation of specialized nutritional support or death, whichever occurred first.
- Please ensure that the CRFs of each patient are complete.
- All data fields should be completed.
    - Please indicate if any given data is not charted on the patient's records.
    - **Asterisk (*) denote required fields.** If required data is not charted on the patient's records, exclude this patient and include the next eligible patient.
- All dates must be recorded in the format YYYY-MM-DD.
- All times must be recorded using the 24 hour (military) clock (HH:MM). Midnight will be 00:00 hr.
- Anywhere in the CRF that "Other, specify" is indicated and/or has been selected, there must be an entry on the line provided further describing what "other" means.
- Day 1 is the date of admission to the study, before Parenteral Nutrition is given.
- **Study days are defined according to ICU chart days (i.e. 07:00-06:59 hrs).** Study days therefore begin and end at 07:00am. This will ease data collection.
    - Day 1 might not be a full 24 hour period.
    - The last day in the ICU might not be a full 24 hour period.

a. Patient Information

Sex*	Place a ✓ in the appropriate box (male or female)
Age*	Record patient's age (year and months)
ICU Admission Date/Time*	Enter the date and time the patient was admitted to the ICU and tick which ICU and site
Hospital	Place a ✓ in the appropriate box to specify which ICU the patient is admitted to.
Type of admission*	Place a ✓ in only one of the following categories: **Medical:** defined as a patient admitted to the ICU for treatment without any surgical intervention (includes patients admitted from a cardiology/ radiology unit) **Surgical:** defined as (1) a patient admitted to the ICU from the operating room directly or a recovery unit following a planned surgical procedure or (2) a patient admitted to the ICU

	from the operating room or a recovery unit following an unplanned surgical procedure. *Note: If a surgical patient develops a medical complication and is transferred to the ICU from the ward, this would be a "medical" admission type.*
Primary ICU diagnosis	Identify and write down the most pertinent diagnosis that resulted in the patient's admission to ICU. Only one diagnosis can be chosen. Remember, symptoms are not an admission diagnosis (e.g. respiratory distress, hypotension, etc.) Example: A patient was admitted to hospital for gut shot abdomen. Post-operatively the patient developed sepsis and was subsequently admitted to the ICU. The patient would be classified as *surgical* admission type, and *sepsis* as the primary ICU diagnosis.
APACHE II score*	The APACHE II score must be calculated using Table 1 Appendix 1. *Note: For each APACHE variable, use the single worst value out of all values from the first 24 hours after ICU admission. If variables are not available from the first 24 hours, go outside the 24 hour window and use data closest to ICU admission.*
SOFA score	The SOFA score must be calculated daily using Table 2 Appendix I
RIFLE classification	The RIFLE classification must be assessed daily using Table 3 Appendix 1

b. Medical follow-up:

Review study participants' ICU charts and chart the following:

- Medication/s
- Other I.V Fluids
- Tests/procedures
- Monitoring parameters
- Laboratory blood values
- Arterial blood gas values
- SOFA score
- RIFLE classification
- Fluid balance
- Gastric aspirates
- Vomiting
- Stools
- Clinical presentation

c. Baseline nutritional assessment

Height*	Record the patient's height charted on his/her ICU chart. If there is no record, measure the patient's height while lying flat in bed.
Weight*	Record the patient's weight charted on his/her ICU chart. When applicable also record the adjustment of body weight for oedema or amputations (if charted).
Body mass index (BMI)	Calculate and indicate the patient's BMI according to charted weight and height.
Nutritional status	Indicate the patient's nutritional status according to the BMI classification system.
Calculation of ideal body weight	Ideal body weight must be calculated for all patients according to the following sex-specific guideline: ***Males:*** Height^2 (m) X 20 – 25 ***Females:*** Height^2 (m) X 19 – 24 *Note: Use the height and weight recorded on the patient's ICU chart/s.* *The "ideal body weight" does not necessarily refer to the weight used in the calculation of nutritional requirements.*

d. Daily Feeding Prescription

Daily feeding prescriptions are routinely calculated by the Dietitian and or attending physician and charted for all ICU patients (charted daily on ICU charts). The daily feeding prescription will be calculated by using the method and formulas specified in Appendix IV. The Parenteral Nutrition (ITN 8807 or ITN 8007) will be ordered for each patient on the study and the administration rate will be adjusted according to the patient's nutritional requirements. Review each study participant's daily feeding prescription from the day of ICU admission until ICU discharge, discontinuation of specialized nutritional support or death, whichever occurred first. Use the patient's daily feeding prescriptions (as charted on his/her ICU charts) to record the following information. Please indicate on the CRF if any particular information was not charted on the patient's records. Remember **Asterisk (*) denote required fields.** If required data is not charted on the patient's records, exclude this patient and include the next eligible patient.

Person responsible for writing daily feeding prescription*	Indicate the person who calculated/wrote the patient's daily feeding prescription; e.g. registered dietician, attending registrar, consultant or chief physician of the ICU.
Nutritional Support Initiation Date/Time*	Enter the date/time PN was initiated in the ICU
Calculation of nutritional requirements	Calculate nutritional requirements according to the method specified in Appendix IV. Daily feeding prescriptions may change over time and should be indicated as

	such.
Prescribed energy intake*	Enter the total kilocalories provided by the **goal regimen** (i.e. maximum rate/volume) for PN or EN/PN. *Note: If a patient received both EN and PN, please record the kilocalories from the combination prescription of EN and PN. If a patient received Propofol, enter the prescription **before** adjusting for Propofol.*
Prescribed protein intake*	Enter the grams provided by the **goal regimen** (i.e. maximum rate/volume) for PN or EN/PN. *ote: If a patient received both EN and PN, please record the protein from the combination prescription of EN and PN.*

e. Retrospective Progress Report

Review the patient's ICU charts and write down short and concise daily progress reports.

5. Daily Biochemical Data

Use Appendix III to retrospectively record the daily biochemical data of each study participant, from ICU admission until discharge, discontinuation of specialized nutritional support or death, whichever occurred first. Retrospective review of ICU charts should be done on consecutive days following ICU admission. If a patient remained in ICU for more than 6 days data should only be collected until day 6 in ICU. Use additional pages of the flow chart as necessary.

Routine blood samples will be taken on admission to ICU (Day 0), immediately prior to starting the PN (Study day 1). 24 hours after initiating PN (Day 2), 48 hours after initiating PN (Day 3) and five days after initiating PN (Day 6). (Study Day 1 is after ICU admission and inclusion into the study, prior to the administration of Parenteral Nutrition until 07:00am the next morning. This might be less than 24 hours. Day 2 and subsequent days are when the patient is receiving PN and labelled according to ICU chart days (i.e. 07:00am to 06:59am). This will ease data collection.

Blood samples should be collected the same time each day via an arterial line. Use the specimen bags provided for each day for the routine bloods as well as special laboratory measurements, which will be kept in the patient file.

Blood gases should be done daily at midday.

Person responsible for taking daily routine bloods	Indicate the person who was responsible for taking routine blood samples e.g. nursing sister, attending registrar
Person responsible for taking blood samples for additional laboratory measurements	Indicate the person who was responsible for taking additional blood samples e.g. attending registrar, consultant
Routine blood measurements	Enter the values of the routine blood measurements, namely; PCT, FBC, U&E, Triglycerides, blood glucose and Liver function tests according to the laboratory results in the case report form.
Additional blood measurements	Enter the values of the additional blood measurements, namely; Plasma Cytokines, Plasma EPA, α-tocopherol and Leukotriene B_5/LTB_4 ratio taken on Study Day 1, 3 and 6, in the case report form. These will only be tested at the end of the study.
Daily blood gases	Enter the values of the blood gases taken daily at midday on the case report form.
Other	Record any other blood tests done during the study period

6. Calculating patients nutritional requirements

It is the dietitian or attending physician's responsibility to calculate the patient's nutritional requirements.

The nutritional requirements need to be calculated for each study participant on a daily basis, according Appendix IV.

The dietitian needs to enter all final calculations into the parenteral nutrition (PN) prescription form (Appendix V) and on the patient's ICU chart.

The PN prescription form needs to be discussed with the clinician and then signed by the dietitian and clinician. This form summarises all the patient's requirements as well as the composition of the PN.

7. Quality Control Form

The quality control form (Appendix VI) forms part of the quality control checks which is the study investigator's responsibility.

The research assistant needs to complete a copy of the form. This form should be kept separately from the screening and CRF.

The pharmacists at Fresenius Kabi Bloemfontein and Johannesburg, also needs to complete a copy of the form.

The information required on the quality control form is:

- Patient's research Number
- Hospital name
- ICU name
- Patient's name
- Patient's hospital number

This form should be completed every time a new patient is entered into the study.

8. Additional Laboratory Measurements request form

The additional laboratory measurements request form (Appendix VII) will be a different colour to the normal laboratory request form. The form will include the patient's details as well as the study's name and ethics approval number. All details pertaining to the sample collection are included on the form.

This form will be placed in a specimen bag with all the tubes needed for that particular day and will be placed in the patient's file.

Once the specimen has been taken, label the tube with the patient's initial and surname and place it in the specimen bag.

Complete the form (appendix VII) and place a ✓ in the column to confirm which blood specimens have been taken.

Place the form in the specimen bag.

The research assistant at each site will be responsible for the additional laboratory measurement, making sure that the measurements are taken according to the study protocol.

At Universitas Hospital she will take all the additional samples to the Haematology research laboratory for storage at -80^{0}C.

The procedure for collecting additional laboratory measurements on the weekend will be as follows; once the samples have been taken, labelled and placed in the specimen bag, they need to be taken to the NHLS depot on the 4th floor, where the samples will be centrifuged and stored at -20^{0}C. These samples will then be collected on the Monday by a staff member and taken to the Haematology research laboratory where they will be stored at -80^{0}C.

The blood sample taken for the α-tocopherol test needs to be covered in foild before it is frozen at -20^{0}C and will be stored at the Haematology department until the study is completed.
At Pelonomi Hospital, the research assistant will then take the specimens to the NHLS laboratory at Pelonomi for centrifuging and storage at 4^{0}C. These samples will be collected by a courier and taken directly to the Haematology research laboratory for storage at -80^{0}C. On the weekend the samples will be kept at Pelonomi and collected by the courier on Monday morning for delivery to the Haematology research laboratory.

At WDGMC, the special laboratory samples will be sent to BARC SA Laboratories to be centrifuged and stored at -80^{0}C.
At CHBAH, the special laboratory samples will be taken by the consultant and centrifuged in the ICU by a technician, placed in 4, 1.5ml storage tubes and sent to the Robert Lipschitz Research Laboratory for storage at -80^{0}C . On weekends the samples will be centrifuged in the ICU and stored immediately in the freezer at -20^{0}C. On Monday morning, the specimens will be delivered to the Research laboratory for storage at -80^{0}C.

The blood samples need to be centrifuged for 5 minutes at 4000rpm.
The samples for the fatty acids (plasma EPA) and LTB5/LTB4 will be centrifuged and either taken to the Haematology research laboratory or the respective laboratories at each site where they will be stored at -80^{0}C.

Appendix AI

Scoring systems

(part of data collection protocol)

Table 1: The APACHE II Severity of Disease Classification System(1)

Physiologic Variable	High Abnormal Range					Low Abnormal Range				
	+4	+3	+2	+1	0	+1	+2	+3	+4	Points
Temperature - rectal (°C)	≥41°	39 to 40.9°		38.5 to 38.9°	36 to 38.4°	34 to 35.9°	32 to 33.9°	30 to 31.9°	≤29.9°	
Mean Arterial Pressure - mm Hg	≥160	130 to 159	110 to 129		70 109		50 to 69		≤49	
Heart Rate (ventricular response)	≥180	140 to 179	110 to 139		70 to 109		55 to 69	40 to 54	≤39	
Respiratory Rate (non-ventilated or ventilated)	≥50	35 to 49		25 to 34	12 to 24	10 to 11	6 to 9		≤5	
Oxygenation: A-aDO_2 **or** PaO_2 (mm Hg) a. FIO_2 ≥0.5 record A-aDO2 b. FIO_2 <0.5 record PaO2	≥500	350 to 499	200 to 349		<200 PO2>70	 PO2 61 to 70		 PO2 55 to 60	 PO2<55	
Arterial pH (preferred) Serum HCO3 (venous mEq/l) (not preferred, but may use if no ABGs)	≥7.7 ≥52	7.6 to 7.69 41 to 51.9		7.5 to 7.59 32 to 40.9	7.33 to 7.49 22 to 31.9		7.25 to 7.32 18 to 21.9	7.15 to 7.24 15 to 17.9	<7.15 <15	
Serum Sodium (mEq/l)	≥180	160 to 179	155 to 159	150 to 154	130 to 149		120 to 129	111 to 119	≤110	
Serum Potassium (mEq/l)	≥7	6 to 6.9		5.5 to 5.9	3.5 to 5.4	3 to 3.4	2.5 to 2.9		<2.5	
Serum Creatinine (mg/dl) Double point score for acute renal failure	≥3.5	2 to 3.4	1.5 to 1.9		0.6 to 1.4		<0.6			
Hematocrit (%)	≥60		50 to 59.9	46 to 49.9	30 to 45.9		20 to 29.9		<20	
White Blood Count (total/mm3) (in 1000s)	≥40		20 to 39.9	15 to 19.9	3 to 14.9		1 to 2.9		<1	
Glasgow Coma Score (GCS) Score = 15 minus actual GCS										
A. Total Acute Physiology Score (sum of 12 above points)										
B. Age points (years) ≤44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; ≥75=6										
C. Chronic Health Points (see below)										
Total APACHE II Score (add together the points from A+B+C)										

Chronic Health Points: If the patient has a history of severe organ system insufficiency or is immunocompromised as defined below, assign points as follows:

5 points for nonoperative or emergency postoperative patients
2 points for elective postoperative patients

***Definitions*:** organ insufficiency or immunocompromised state must have been evident **prior** to this hospital admission and conform to the following criteria:

- **Liver** – biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.
- **Cardiovascular** – New York Heart Association Class IV.
- **Respiratory** – Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction (i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg), or respirator dependency.
- **Renal** – receiving chronic dialysis.
- **Immunocompromised** – the patient has received therapy that suppresses resistance to infection (e.g., immunosuppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS).

Interpretation of Score:

Score	Death Rate (%)
0-4	4
5-9	8
10-14	15
15-19	25
20-24	40
25-29	55
30-34	75
>34	85

Table 2: Sequential Organ Failure Assessment (SOFA) Score (2)

SOFA score	1	2	3	4
Respiration PaO_2/FiO_2, mmHg	<400	<300	<200	<100 with respiratory support
Coagulation Platelets $\times 10^3/mm^3$	<150	<100	<50	<20
Liver Bilirubin, mg/dl (μmol/l)	1.2 – 1.9 (20 – 32)	2.0 – 5.9 (33 – 101)	6.0 – 11.9 (102 – 204)	>12.0 (<204)
Cardiovascular Hypotension	MAP < 70 mmHg	Dopamine ≤5 or dobutamine (any dose)[a]	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system Glasgow Coma Score	13 – 14	10 – 12	6 – 9	<6
Renal Creatinine, mg/dl (μmol/l) or urine output	1.2 – 1.9 (110 – 170)	2.0 – 3.4 (171 – 299)	3.5 – 4.9 (300 – 440) or <500 ml/day	>5.0 (>440) or <200 ml/day

[a] Adrenergic agents administered for at least 1 h (doses given are in μg/kg·min)

Table 3: RIFLE Classification (3)

	GFR Criteria	Urine Output Criteria
Risk	Increased SCreat X 1.5 or GFR decrease >25%	UO<5ml/kg/hr X 6 hr
Injury	Increased SCreat X 2 or GFR decrease >50%	UO<5ml/kg/hr X 12 hr
Failure	Increased SCreat X 3 or GFR decrease75% or SCreat ≥4mg/dl Acute rise ≥3.5mg/dl	UO<3ml/kg/hr X 24 hr or Anuria X 12hrs
Loss	Persistent Acute renal failure = complete loss of kidney function > 4 weeks	
End stage kidney failure	End Stage Kidney Disease (>3months)	

Table 4: ARDS Berlin Definition (4)

The Berlin definition of acute respiratory distress syndrome	
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities — not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mmHg < PaO_2/FIO_2 ≤300 mmHg with PEEP or CPAP ≥5 cmH_2O[c]
Moderate	100 mmHg < PaO_2/FIO_2 ≤200 mmHg with PEEP ≥5 cmH_2O
Severe	PaO_2/FIO_2 ≤100 mmHg with PEEP ≥5 cmH_2O

Abbreviations: CPAP, continuous positive airway pressure; F_IO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; [a]Chest radiograph or computed tomography scan; [b]If altitude is higher than 1,000 m, the correction factor should be calculated as follows: [PaO_2/FIO_2_(barometric pressure/760)]; [c]This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Appendix AII:

Screening log

(part of data collection protocol)

SCREENING LOG

Hospital Name:_____

Multi / Surgical ICU

Please use additional copies of this page as necessary.

Screening number	Date of screening	Date of discharge/demise (specify)	Date of admission	Patient initials for all patients discharged from ICU or who demised on/after first day of data collection	Patient hospital number	Patient is ≥ 18 years old	Patient has SIRS and/or Sepsis	Patient does not acute hepatitis and or ,cirrhotic liver	Patient does not have chronic renal failure and/or end stage renal disease	No know allergic reaction against fish or egg proteins	Patient with ARDS	Patient planned to receive PN for at least 5 days.	Patient eligible?	Research number
e. g.	*20/1*	*26/1*	*21/1*	*P Nel*	*92724*	✓	✓	✓	✓	✓	✓	✓	*Y*	*R1*
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														
11														
12														
13														
14														
15														
16														
17														
18														
19														
20														
21														
			TOTAL ELIGIBLE: _____											

SCREENING LOG

Hospital Name:_____

Multi / Surgical ICU

Please use additional copies of this page as necessary.

Screening number	Date of screening	Date of discharge/demise (specify)	Date of admission	Patient initials for all patients discharged from ICU or who demised on/after first day of data collection	Patient hospital number	Patient is ≥ 18 years old	Patient has SIRS and/or Sepsis	Patient does not acute hepatitis and or ,cirrhotic liver	Patient does not have chronic renal failure and/or end stage renal disease	No know allergic reaction against fish or egg proteins	Patient with ARDS	Patient planned to receive PN for at least 5 days.	Patient eligible?	Research number
e. g.	*20/1*	*26/1*	*21/1*	*P Nel*	*92724*	✓	✓	✓	✓	✓	✓	✓	*Y*	*R1*
22														
23														
24														
25														
26														
27														
28														
29														
30														
31														
32														
33														
34														
35														
36														
37														
38														
39														
40														
41														
42														
			TOTAL ELIGIBLE: _____											

SCREENING LOG

Hospital Name:_____

Multi / Surgical ICU

Please use additional copies of this page as necessary.

Screening number	Date of screening	Date of discharge/demise (specify)	Date of admission	Patient initials for all patients discharged from ICU or who demised on/after first day of data collection	Patient hospital number	Patient is ≥ 18 years old	Patient has SIRS and/or Sepsis	Patient does not acute hepatitis and or ,cirrhotic liver	Patient does not have chronic renal failure and/or end stage renal disease	No know allergic reaction against fish or egg proteins	Patient with ARDS	Patient planned to receive PN for at least 5 days.	Patient eligible?	Research number
e. g.	*20/1*	*26/1*	*21/1*	*P Nel*	*92724*	*`1*	✓	✓	✓	✓	✓	✓	*Y*	*R1*
43														
44														
45														
46														
47														
48														
49														
50														
51														
52														
53														
54														
55														
56														
57														
58														
59														
60														
61														
62														
63														
			TOTAL ELIGIBLE: _____											

SCREENING LOG

Hospital Name:_____

Multi / Surgical ICU

Please use additional copies of this page as necessary.

Screening number	Date of screening	Date of discharge/demise (specify)	Date of admission	Patient initials for all patients discharged from ICU or who demised on/after first day of data collection	Patient hospital number (GT/GP no)	Patient is ≥ 18 years old	Patient has SIRS and/or Sepsis	Patient does not acute hepatitis and or ,cirrhotic liver	Patient does not have chronic renal failure and/or end stage renal disease	No know allergic reaction against fish or egg proteins	Patient with ARDS	Patient planned to receive PN for at least 5 days.	Patient eligible?	Research number
e. g.	*20/1*	*26/1*	*21/1*	*P Nel*	*GP0092724*	✓	✓	✓	✓	✓	✓	✓	*Y*	*R1*
64														
65														
66														
67														
68														
69														
70														
71														
72														
				TOTAL ELIGIBLE: _____										

Appendix AIII:

Case Report Form

(part of data collection protocol)

Case Report Form

Research number: **e.g. R1**

A. PATIENT INFORMATION

Sex*: ☐ Male ☐ Female **Age*** (year & months): _____

ICU Admission Date*: (YYYY-MM-DD):_____ Time: (HH:MM, 24h): _____

Hospital: Universitas ICUs: Multi ☐ Surgical ☐ **Pelonomi** ICU ☐ WDGMC ☐ CHBAH ☐

Type of admission: ☐ Medical ☐ Surgical

Primary ICU diagnosis*:_____
_____
_____
_____

Other comorbidities or medical/nutritional problems: _____
_____
_____
_____
_____
_____
_____
_____

Medical history: _____
_____
_____
_____
_____
_____

APACHE II SCORE:*_____

MEDICAL FOLLOW-UP

Medication

Medication e.g. Propofol	Dose	Date						

I.V Fluids administered		Date						

Date	Test/ Procedure	Results

Monitoring Parameters		Date						
Parameter	Normal range							
Blood Pressure								
Temperature								
Heart rate								

Laboratory blood values								
Parameter	Normal range	Date						
WCC	4.0 –10X10^9/L							
Hb	12.0 – 15.0g/dL							
Plt	178-40X10^9/L							
CRP	<10							
PCT	<0.5							
Na	135- 145							
K	3.3 – 5.3							
Cl	99 – 113							
CO_2	18 – 29							
Urea	2.6 – 7.0							
Creat	60 – 100							
GFR								
Ca	2.05 – 2.56							
Mg	0.65 – 1.1							
P	0.8 – 1.4							
Glucose	3 – 10mmol/L							
Triglycerides								
ALT								
AST								
TNF-α								
IL-1β								
IL-6								
IL-10								
Plasma EPA levels								
LTB5/LTB4 ratio								
Alpha tocopherol								
Arterial blood gas		**Date**						
pH	7.35 – 7.45							
pCO_2	35-45 mm Hg							
pO_2	80-100 mmHg							
HCO_3	21-28 mEq/L							
BE	-4 - +2							
O_2 saturation	95% - 100%							
PaO_2/FiO_2 ratio								
Mean Airway Pressure	cm H_20							
SOFA Score	0							
RIFLE Classification								

Other parameters

Fluid balance	Intake*								
	Output*								
	Balance*								
Gastric aspirates		<200mL							
Stools		<400mL							
Urine output									
Vomiting									

Clinical presentation

C. BASELINE NUTRITIONAL ASSESSMENT

Date recorded on ICU chart:_____ (Day of ICU stay: ____)

Height (metres):*_____ **Weight** (kg):*_____ Actual ☐

Estimated ☐

Weight adjusted for oedema?* ☐ No ☐ Not charted ☐

If yes, indicate degree of oedema: ☐ Moderate ☐ Severe ☐ Not charted ☐

If yes, show calculations (if charted):

_____

_____

Dry weight: _____kg ☐ Not charted

Weight adjusted for amputations?* Yes ☐ No ☐ Not charted ☐

If yes, indicate body parts amputated: _____ Not charted ☐

If yes, show calculations (if charted):

_____

_____

Adjusted weight: _____kg ☐ Not charted

Body mass index:*_____kg/m^2 Actual Wt ☐

Estimated Wt ☐

Nutritional status* (tick the appropriate block)**:**

	Undernourished	*Grade I*	17 ≤ BMI < 18.5
		Grade II	16 ≤ BMI < 17
		Grade III	BMI < 16
	Normal		18.5 ≤ BMI < 25
	Overweight		25 ≤ BMI < 30
	Obese	*Class I*	30 ≤ BMI < 35
		Class II	35 ≤ BMI < 40
		Class III (Morbid obesity)	BMI ≥ 40

Calculation of ideal body weight:

Males: Height^2 (m) X 20 – 25

Show calculations:_____

Females: Height^2 (m) X 19 - 24

Show calculations:_____

D. NUTRITIONAL PRESCRIPTION					
Date	**Energy***	**PROT***	**CHO**	**Lipid**	**Feeding prescription**
Date: _____ Day of ICU stay: _____ Responsible person: _____			**Glucose oxidation:**	**Max lipids:**	Volume/24hr*: _____ Rate/hr*: _____ **Prescribed energy intake (kcal/day):*** _____ **Prescribed protein intake (g/day):*** _____
Date: _____ Day of ICU stay: _____ *Reason for changing prescription:* _____ Responsible person: _____			**Glucose oxidation:**	**Max lipids:**	Volume/24hr*: _____ Rate/hr*: _____ **Prescribed energy intake (kcal/day):*** _____ **Prescribed protein intake (g/day):*** _____
Date: _____ Day of ICU stay: _____ *Reason for changing prescription:* _____ Responsible person: _____			**Glucose oxidation:**	**Max lipids:**	Volume/24hr*: _____ Rate/hr*: _____ **Prescribed energy intake (kcal/day):*** _____ **Prescribed protein intake (g/day):*** _____

Date: _____ Day of ICU stay: _____ *Reason for changing prescription:* _____ Responsible person: _____			**Glucose oxidation:**	**Max lipids:**	Volume/24hr*: _____ Rate/hr*: _____ **Prescribed energy intake (kcal/day):*** _____ **Prescribed protein intake (g/day):*** _____

Date: _____ Day of ICU stay: _____ *Reason for changing prescription:* _____ Responsible person: _____			**Glucose oxidation:**	**Max lipids:**	Volume/24hr*: _____ Rate/hr*: _____ **Prescribed energy intake (kcal/day):*** _____ **Prescribed protein intake (g/day):*** _____

E. PROGRESS REPORT

Date	**Follow-up notes**

Appendix AIV

Calculation of Nutritional Requirements

(part of data collection protocol)

Calculation of Nutritional requirements:

It is very important that the dietitian follows the procedure below in calculating patient's nutritional requirements to make sure that the same procedure is used on every patient.

The following procedure should be followed to calculate the patient's nutritional requirements:

1. Record the patient's actual or estimated weight according to the CRF (Appendix III)

2. Record the calculated BMI for the patient.

3. Use the table below as a guide to which body weight should be used for the calculations of energy

Weight	Indication for use
Actual BW	Underweight (at risk of *refeeding syndrome*)
(Actual BW + ideal BW based on a BMI 18.5 kg/m^2) X 0.5	Underweight (no risk of *refeeding syndrome*)
Actual BW	Normal weight
Ideal BW based on a BMI of 24.9 (upper range of normal)	Overweight
(Actual BW – ideal BW based on a BMI of 24.9 kg/m^2) X 0.25} + ideal BW	Obese

For Example 1: Patient R20 has a BMI of 22 and estimated body weight = 68kg.
Use 68kg in all the calculations.

Example 2: Patient R25 has a BMI of 29 and actual body weight = 82kg and height of 1.68m
Use IBW based on BMI of 24.9 (upper range of normal) = 70 kg

4. To calculate energy, use the equation below. Only non-protein energy (NPE) is going to be used in the calculation

   The carbohydrate (CHO) and lipid requirements are then calculated from the NPE. Carbohydrates usually provided as 50 – 60% of the NPE and lipid, 40 – 50% NPE.

   When calculating your grams of CHO and lipid remember that 1g CHO provides 4kcal and 1g lipid provides 9kcal.

   Calculate the patient's maximum glucose oxidation rate at **4-5mg/kg/min**, as well as the initial rate at **2.5mg/kg/min**. Make sure that your total amount of CHO does not exceed this limit. This will enable you to cross check your calculations and make sure that you do not overfeed the patient.

   Calculate the patient's maximum lipid intake: **1-2g/kg/day.**

Nutritional requirement	Calculation	Example
Energy Requirements as NPE:	25 – 30kcal/kg/day	Example 1: Patient R20 BMI = 22 and estimated weight = 68kg NPE = (25 – 30) X 68 = 1700 – 2040 kcal/day Example 2: Patient R25, Use 70kg in calculations NPE: = (25 – 30) X 70 = 1750 – 2100kcal/day
CHO Requirements (expressed as g/day) Maximum glucose oxidation rate Initial glucose oxidation rate	50 – 60% NPE 4-5mg/kg/min 2.5mg/kg/min	Example 1: Patient R20 NPE = 1700 – 2040 kcal/day CHO req = 50-60% NPE = 50% (1700-2040) – 60% (1700-2040) = (850-1020) – 1020 – 1224) Divide by 4kcal to get grams CHO = (850-1020)/4 – (1020 – 1224)/4 = 212 – 306g CHO Max Glucose oxidation rate: 4-5mg/kg/min = [(4 - 5) X 68 X 1440]/1000 = 391 – 490g glucose Initial glucose oxidation rate: 2.5mg/kg/min = [2.5 X 68 X 1440]/1000 = 288g
Lipid Requirements (expressed as g/day) Maximum lipid intake	40 – 50% NPE 1 - 2g/kg/day	Example 1: Patient R20 NPE = 1700 – 2040 kcal/day Lipid req =40 - 50% NPE = 40% (1700-2040) – 50% (1700-2040) = (680 – 816) - (850-1020) Divide by 9kcal to get grams lipid = (680 – 816)/9 - (850-1020)/9 = 75g – 113g Maximum lipid intake: 1-2g/kg/day = 68 – 136g/day

5. To calculate protein and nitrogen use the equation below. Remember protein requirements are always calculated using ideal body weight or actual body weight if the BMI = 19 – 24.9kg/m^2

Protein Requirements (expressed as g/day).	Use 1.5 - 2g/kg/day	Example 1: Patient R20 BMI = 22 Estimated weight 68kg Protein req = 1.5 – 2g/68kg/day = 102 – 136g /day Example 2: Patient R25, BMI = 29 actual body weight = 82kg IBW = Ht in m^2 X 20 – 25 = $(1.68)^2$ X 20 – 25 = 2.8224 X 20 – 25 = 56.5 – 70.56kg = average 64kg Protein req = 1.5 – 2g/64kg/day = 96g – 128g/day
Nitrogen Requirements (expressed in g/day)	1g Nitrogen = 6.25g protein, therefore divide the protein requirements by 6.25 to get Nitrogen requirements	Example 1: Patient R20 Protein req = 102 – 136g /day Nitrogen req = (102 – 136)/6.25 = 16.32 – 21.76gN Example 2: Patient R25 Protein req = 96g – 128g/day Nitrogen req = (96 – 128)/6.25g = 15.36 – 20.48gN

6. To calculate the fluid requirements, use the equation below. Fluid is always calculated on ideal body weight. Remember to take into consideration other I.V fluids that the patient is receiving. You must also consider any additional fluid losses, i.e fistula output or additional fluid requirements, i.e. raised temperature. Always consult with the attending physician in terms of the fluid availability for PN.

Fluid requirements (expressed as ml/kg/hr) Add losses due to fever Take into account other losses,e.g.fistula output	1.5ml/kgIBW/hr + 2 – 2,5ml/kg/1^{0}C > 37^{0}C	Example 1: Patient R20 BMI = 22 Estimated weight 68kg Fluid req: 1.5 X 68 = 102ml/hr = 2448ml/day Example 2: Patient R25, BMI = 29 IBW = 56.5 – 70.56kg = average 64kg Fluid reg: 1.5 X (64 – 70) = 96 – 105ml/hr = 2304 – 2520ml

7. The final step is to use the above calculations to determine the rate of the PN to be used in the study (ITN 8807 or ITN 8007). The composition of ITN 8807 and ITN 8007 is as follows:

Contents of PN	ITN 8807	ITN 8007
Fluid	2390ml	2390ml
Energy (NPE)*	1800kcal	1800kcal
Carbohydrates	200g (45% of NPE)	200g (45% of NPE)
Fat	100g (55% of NPE)	100g (55% of NPE)
Nitrogen	16.8g	16.8g
Glutamine	15g	15g
Vitamins, minerals and trace elements	RDA **	RDA**
Osmolarity	981mOsm/l	978mOsm/l

Example 1: Nutritional Requirements for patient R20

Nutritional Requirements	Patient R20 requirements	100ml/hr of ITN 8807/ITN 8007 provides
Energy	1700 - 2040 kcal	1800kcal
CHO	212 – 306g Max glucose oxidation: 391 – 490g Initial glucose oxidation: 288g	200g
Lipid	75 – 113g Maximum lipid: 68 – 136g	100g
Protein Nitrogen	102 – 136g 16.32 – 21.76g	 16.8g
Glutamine		15g
Vitamin, minerals and trace elements	RDA	RDA
Fluid	2448ml	2390

Appendix AV

Parenteral Nutrition Prescription Form

(part of data collection protocol)

Parenteral Nutrition Prescription form

Hospital :	Ward :	Date:

Patient Name	Patient Hospital No.	Research No.

Nutritional Requirements	Patient	ITN 8807/ITN 8007 provides	Determined rate of PN to meet patient's requirements
Energy		1800kcal	
CHO		200g	
Lipid		100g	
Nitrogen		16.8g	
Glutamine		15g	
Vitamin, minerals and trace elements		RDA	
Fluid		2390	

Additional comments _____:

_____

_____

_____

Signed by: _____ Date: _____
Dietitian

Signed by:_____ Date:_____
Clinician

Appendix AVI

Quality Control Form

(part of data collection protocol)

Quality Control Form

Patient Research Number	Hospital Name	ICU Name	Patient Name	Patient Hospital Number
R1				
R2				
R3				
R4				
R5				
R6				
R7				
R7				
R8				
R9				
R10				
R11				
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Patient Research Number	Hospital Name	ICU Name	Patient Name	Patient Hospital Number
R41				
R42				
R43				
R44				
R45				
R46				
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R71				
R72				

Appendix AVII

Additional Laboratory Measurements Request Form

(part of data collection protocol)

Specialised Haemostasis Research Laboratory

Please do not register at NHLS WDGMC
These are research samples

Test request form

Patient details / sticker Ethics approval No

Patient Name:		Clinical and project details: To investigate the effect of a fish oil containing parenteral lipid emulsion on inflammatory markers, gas exchange and clinical outcomes in septic patients
Patient Research Number:		

Blood Sample	Place a √ to confirm the sample has been taken
TNF-α	
IL-1β	
IL-6	
IL-10	
EPA	
LTB5/LTB4 ratio	

1. Spin yellow top tubes for 5 minutes at 4000rpm
2. Pour into 4 1,5ml Send-away tubes
3. Paste a small number on every Send-away tube as well as on the form
4. DO NOT REGISTER!!
5. *Put corresponding form with specimens immediately in a plastic bag into the basket provided in the walk-in freezer at -20^{0}C*
6. These specimens will fetched and taken to the BARC Laboratory

Name of Study Leader / Research assistant
Contact no:
Date: Time:

References:

1. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: A severity of disease classification system. Crit Care Med. 1985;13(10):818-29.
2. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22:707-10.
3. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8:R204-R12.
4. Fanelli V, Vlachou A, Ghannadian S, et al. Acute Respiratory distress syndrome: new derinition, current and future therapeutic options. J Thorac Dis. 2013;5(3):326-34.

Appendix B

Screening Information Leaflet and Consent Form

SCREENING INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE RESEARCH PROJECT:
To investigate the effect of a fish oil containing parenteral lipid emulsion on inflammatory markers, gas exchange and clinical outcomes in septic patients

REFERENCE NUMBER: M14111090

PRINCIPAL INVESTIGATOR: Mrs Veronique Donoghue

ADDRESS: 7 Third Avenue,

Parktown North

Johannesburg

CONTACT NUMBER: 0833864001

Hello, my name is _____. I am a research assistant helping out with a research project, which is part of a Masters degree in Human Nutrition at the University of Stellenbosch. This ICU is participating in the above research project. This study aims to compare the difference between two fats (oils) as part of specialized feeding directly into the patient's veins.

Do you or your relative have any objection to me reviewing your ICU chart to determine if you fit the criteria to be involved in this study? Yes ☐ ☐

If you are a suitable candidate, I will explain all the information about the study to you or your relative. Your participation or your relative's participation, is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever

Signed at (*place*) .....…….. on (*date*) ……...…….. 2016.

…….. ……..
Signature of participant or relative **Signature of witness**

PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM FOR WDGMC

TITLE OF THE RESEARCH PROJECT:
To investigate the effect of a fish oil containing parenteral lipid emulsion on inflammatory markers, gas exchange and clinical outcomes in septic patients

REFERENCE NUMBER: M14111090

PRINCIPAL INVESTIGATOR: Mrs Veronique Donoghue

ADDRESS: 7 Third Avenue,

Parktown North

Johannesburg

CONTACT NUMBER: 0833864001

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study is part of my Masters degree in Human Nutrition at the University of Stellenbosch. I am a registered dietitian with the BSc Dietetics and a Post Graduate Degree in Hospital Dietetics.

This study has been approved by the **Health Research Ethics Committee at Stellenbosch University, Free State University and University of the Witwatersrand** and will be conducted according to the ethical guidelines and principles of the International Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

The study will be conducted in Intensive Care Unit (ICU) at Wits Donald Gordon Medical Centre in Johannesburg.

A total of 66 participants will be recruited.

This study aims to compare the difference between two fats (oils) as part of specialized feeding directly into the patient's veins. This is called intravenous feeding. This specialized feeding is used in the intensive care when the patients are extremely ill, i.e. they are unable to eat and sometimes can't breathe on their own (on a ventilator). This specialized feeding is used when the patient is unable to tolerate any other form of feeding and is used quite safely all over the country and the world. There has been some promising new information about providing intravenous fats that contain fish oil to intensive care patients, showing that they can reduce the risk of infection and

improve the patient's outcome. This study will be comparing two types of intravenous fats and assessing the outcome.

You have been asked to be part of this study because you are an adult (>18 yrs) male or female, who have been admitted to the ICU with infections (sepsis) and you are unable to eat on your own and will be given intravenous (parenteral) nutrition (PN) for more than 5 days.

If you agree to participate in the study the following will happen:

1. The research staff would need access to your ICU chart and records for your blood results and information regarding your treatment.
2. Extra bloods would need to be taken from you on Day 1, 3 and 6 of the study. These bloods will be taken at the same time as the usual bloods needed for your treatment.
3. You will be requested to read and complete the consent form.

Once you have consented, you will be allocated a research number to make sure that all your records will be treated with strict confidentiality. Only then will the research assistant start collecting information about you. The dietitian will be consulted to do a nutritional assessment on you and will calculate your nutritional requirements to make sure you receive the correct nutrition. This nutrition will be administered directly into your veins according to the procedures in the hospital intensive care units. The randomization to decide which PN bag you will receive, will take place at the facility that dispenses the PN to the hospitals.

You will be receiving a PN prescription either containing a soybean based oil (Intralipid ® ITN 8007) or a fish oil-containing oil (SMOFlipid® ITN 8807). Both of these PN solutions are used regularly in the ICUs. By following the above procedure it is clear that there will be no deviation from usual standardized prescription techniques. The only exception being the specific PN bag that you will receive based on the fat composition thereof.

The study period is 5 days on PN, after this period your treatment will continue, however the PN prescription will no longer be blinded. You will be monitored throughout the study period according to the study protocol as well as the ICU protocol.

Why have you been invited to participate?

You have been invited to participate in the study because you are over the age of 18 years. You have been admitted to the ICU at Wits Donald Gordon Medical Centre. You have been diagnosed with sepsis, you are unable to eat on your own and you will require PN for more than 5 days.

If you were unable to give consent initially to participate in the study, your closest relatives will be asked to give consent. Once you are able you will be asked again for your consent. If you then do not want to participate or you do not want your information to be used, all the documents will be destroyed immediately. The results of the study will be published. Feedback on the results and outcome of the study will be made available on request by yourself or your closest relative.

Will you benefit from taking part in this research?

Taking part in the study will not provide any personal benefit to you whilst being in ICU, however it will provide more information on specialized intravenous fats as part of PN and future ICU patients requiring this nutritional support will benefit from the knowledge gained.

Are there any risks involved in your taking part in this research?

There are minimal risks involved in participating in the study. All the products being used have been registered and have been available on the market and used successfully for a substantial amount of time. You will be monitored closely throughout your stay in the ICU.

If you do not agree to take part, what alternatives do you have?

If you do not agree to participate in the study, you will continue to receive treatment according to the ICU protocol. It will not affect your medical management in any way.

Who will have access to your medical records?

Your ICU doctor and staff will have access to all your records. However confidentiality is protected within the hospital at all times. In terms of the study, you will remain completely anonymous. A research number will be allocated to you at the beginning of the study. This number will be used on all the data collections sheets, by the research assistant. The primary investigator will receive all the forms with your research number and no other personal details . The form linking your name to your research number will be kept in a locked cabinet at the respective hospitals with only one person having access to the key.

What will happen in the unlikely event of some form of injury occurring as a direct result of your taking part in this research study?

Throughout the study standard procedures will be used, to make sure that there are minimal errors. However, all patients participating in this study will be covered by an insurance policy.

Will you be paid to take part in this study and are there any costs involved?

No, you will not be paid to take part in the study, because you are already admitted to the ICU. With regard to the nutritional treatment (PN) there will be no costs involved for you, if you do take part. This study does not affect the rest of your usual management and thus you will still be responsible for the payment of that section as per usual.

Is there anything else that you should know or do?

- You can contact Dr Schleicher at telephone no. 011 726 7403 if you have any further queries or encounter any problems or Veronique Donoghue at 0833864001.
- You can contact the Health Research Ethics Committee at 011 7171252 if you have any concerns or complaints that have not been adequately addressed by your study doctor.
- You will receive a copy of this information and consent form for your own records.

Declaration by participant

By signing below, I ……..……. agree to take part in a research study entitled "*To investigate the effect of a fish oil containing parenteral lipid emulsion on inflammatory markers, gas exchange and clinical outcomes in septic patients"*

I declare that:

- I have read or have had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) .....…..…….. on (*date*) ……...…….. 2016.

…….. ……..

Signature of participant **Signature of witness**

Declaration by family member on behalf of participant (if applicable)

By signing below, I ……..……. agree to let my family member *(name)*…….. take part in a research study entitled "*To investigate the effect of a fish oil containing parenteral lipid emulsion on inflammatory markers, gas exchange and clinical outcomes in septic patients".*

I declare that:

- I have read or have had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that letting my family member take part in this study is **voluntary** and I have not been pressurised to let them take part.
- My family member may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- My family member may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in his/her best interests, or if he/she does not follow the study plan, as agreed to.

Signed at (*place*) .....…..…….. on (*date*) ……...…….. 2016.

……. …….

Signature of family member **Signature of witness**

Declaration by Clinical Head (if applicable)

By signing below, I ……..……. agree to let the patient *(name)*…….. take part in a research study entitled "*To investigate the effect of a fish oil containing parenteral lipid emulsion on inflammatory markers, gas exchange and clinical outcomes in septic patients".*

I declare that:

- I have read the study protocol with the inclusion and exclusion criteria and agree that the patient is eligible to participate in the study.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that letting the patient take part in this study is **voluntary** and I have not been pressurised to let them take part.
- The patient may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- The patient may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in his/her best interests, or if he/she does not follow the study plan, as agreed to.

Signed at (*place*) .....…..…….. on (*date*) ……...…….. 2016.

…….. ……..

Signature of Clinical Head **Signature of witness**

Declaration by investigator

I *(name)* ……..…… declare that:

- I explained the information in this document to ……..
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use an interpreter. (*If an interpreter is used then the interpreter must sign the declaration below.*

Signed at (*place*) .....…..…….. on (*date*) ……...…….. 2016.

…….
Signature of investigator

…….
Signature of witness

Declaration by interpreter

I *(name)* ……..…… declare that:

- I assisted the investigator (*name*) …….. to explain the information in this document to (*name of participant*) ……..…….. using the language medium of Afrikaans/Sotho.
- We encouraged him/her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at (*place*) .....…..…….. on (*date*) ……...……2016

…….. ……..

Signature of interpreter **Signature of witness**

PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM FOR RELATIVES WITH FAMILY AT WDGMC

TITLE OF THE RESEARCH PROJECT:
To investigate the effect of a fish oil containing parenteral lipid emulsion on inflammatory markers, gas exchange and clinical outcomes in septic patients

REFERENCE NUMBER: M14111090

PRINCIPAL INVESTIGATOR: Mrs Veronique Donoghue

ADDRESS: 7 Third Avenue,

Parktown North

Johannesburg

CONTACT NUMBER: 0833864001

Your relative has being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how your relative could be involved. Also, your relative's participation is **entirely voluntary** and you are free to decline to participate, on behalf of your relative. If you say no, this will not affect your relative negatively in any way whatsoever. You are also free to withdraw your relative from the study at any point, even if you do agree for them to take part.

This study is part of my Masters degree in Human Nutrition at the University of Stellenbosch. I am a registered dietitian with the BSc Dietetics and a Post Graduate Degree in Hospital Dietetics.

This study has been approved by the **Health Research Ethics Committee at Stellenbosch University, Free State University and University of the Witwatersrand** and will be conducted according to the ethical guidelines and principles of the International Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

The study will be conducted in Intensive Care Unit (ICU) at Wits Donald Gordon Medical Centre in Johannesburg.

A total of 66 participants will be recruited.

This study aims to compare the difference between two fats (oils) as part of specialized feeding directly into the patient's veins. This is called intravenous feeding. This specialized feeding is used in the intensive care when the patients are extremely ill, i.e. they are unable to eat and usually can't breathe on their own (on a ventilator). This specialized feeding is used when the patient is unable to tolerate any other form of feeding and is used quite safely all over the country and the world. There has been some promising new information about providing intravenous fats that

contain fish oil to intensive care patients, showing that they can reduce the risk of infection and improve the patient's outcome. This study will be comparing two types of intravenous fats and assessing the outcome.

Your relative has been asked to be part of this study because they are an adult (>18 yrs) male or female, who has been admitted to the ICU with infections (sepsis) and is unable to eat on their own and will be given intravenous (parenteral) nutrition (PN) for more than 5 days.

If you agree for your relative to participate in the study the following will happen:

4. The research staff would need access to your relatives ICU chart and records for their blood results and information regarding their treatment.
5. Extra bloods would need to be taken from your relative on Day 1, 3 and 6 of the study. These bloods will be taken at the same time as the usual bloods needed for their treatment.
6. You will be requested to read and complete the consent form on behalf of your relative.

Once you have consented, your relative will be allocated a research number to make sure that all their records will be treated with strict confidentiality. Only then will the research assistant start collecting information about your relative. The dietitian will be consulted to do a nutritional assessment on your relative and will calculate their nutritional requirements to make sure they receive the correct nutrition. This nutrition will be administered directly into your relative's veins according to the procedures in the hospital intensive care units. The randomization to decide which PN bag your relative will receive, will take place at the facility that dispenses the PN to the hospitals.

.

Your relative will be receiving a PN prescription either containing a soybean based oil (Intralipid ®

ITN 8007) or a fish oil-containing oil (SMOFlipid® ITN 8807). Both of these PN solutions are used regularly in the ICUs. By following the above procedure it is clear that there will be no deviation from usual standardized prescription techniques. The only exception being the specific PN bag that you will receive based on the fat composition thereof.

The study period is 5 days on PN, after this period your relatives treatment will continue, however the PN prescription will no longer be blinded. Your relative will be monitored throughout the study period according to the study protocol as well as the ICU protocol.

Why has your relative been invited to participate?

Your relative has been invited to participate in the study because your relative is over the age of 18 years. Your relative has been admitted to ICU at Wits Donald Gordon Medical Centre. They have been diagnosed with sepsis, are unable to eat on their own and will require PN for more than 5 days.

If your relative was unable to give consent initially to participate in the study, you will be asked to give consent. Once your relative is able they will be asked again for their consent. If your relative then does not want to participate or does not want their information to be used, all the documents will be destroyed immediately. The results of the study will be published. Feedback on the results and outcome of the study will be made available on request by yourself or your relative.

Will your relative benefit from taking part in this research?

Taking part in the study will not provide any personal benefit to your relative whilst being in ICU, however it will provide more information on specialized intravenous fats as part of PN and future ICU patients requiring this nutritional support will benefit from the knowledge gained.

Are there any risks involved in your relative taking part in this research?

There are minimal risks involved in participating in the study. All the products being used have been registered and have been available on the market and used successfully for a substantial amount of time. Your relative will be monitored closely throughout your stay in the ICU.

If you do not agree to take part, what alternatives do you have?

If you do not agree to let your relative participate in the study, they will continue to receive treatment according to the ICU protocol. It will not affect their medical management in any way.

Who will have access to your relative's medical records?

Your ICU doctor and staff will have access to all your relative's records. However confidentiality is protected within the hospital at all times. In terms of the study, your relative will remain completely anonymous. A research number will be allocated to them at the beginning of the study. This number will be used on all the data collections sheets, by the research assistant. The primary investigator will receive all the forms with your relative's research number and no other personal details . The form linking your relatives name to their research number will be kept in a locked cabinet at the respective hospitals with only one person having access to the key.

What will happen in the unlikely event of some form of injury occurring as a direct result of your relative taking part in this research study?

Throughout the study standard procedures will be used, to make sure that there are minimal errors. However, all patients participating in this study will be covered by an insurance policy.

Will your relative be paid to take part in this study and are there any costs involved?

No, your relative will not be paid to take part in the study, because they are already admitted to the ICU. With regard to the nutritional treatment (PN) there will be no costs involved for your relative, if they do take part. This study does not affect the rest of your relative's usual management and thus they will still be responsible for the payment of that section as per usual.

Is there anything else that you should know or do?

- You can contact Dr Dr Schleicher at telephone no. 011 726 7403 if you have any further queries or encounter any problems or Veronique Donoghue at 0833864001.
- You can contact the Health Research Ethics Committee at 011 7171252 if you have any concerns or complaints that have not been adequately addressed by your study doctor.
- You will receive a copy of this information and consent form for your own records.

Declaration by family member on behalf of participant (if applicable)

By signing below, I …….. agree to let my family member *(name)*…….. take part in a research study entitled "*To investigate the effect of a fish oil containing parenteral lipid emulsion on inflammatory markers, gas exchange and clinical outcomes in septic patients".*

I declare that:

- I have read or have had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that letting my family member take part in this study is **voluntary** and I have not been pressurised to let them take part.
- My family member may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- My family member may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in his/her best interests, or if he/she does not follow the study plan, as agreed to.

Signed at (*place*) ..... on (*date*) …….. 2015.

…….. ……..

Signature of family member **Signature of witness**

Declaration by investigator

I *(name)* …… declare that:

- I explained the information in this document to ……..
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use an interpreter. (*If an interpreter is used then the interpreter must sign the declaration below.*

Signed at (*place*) ……. on (*date*) …….. 2015.

…….
Signature of investigator

…….
Signature of witness

Declaration by interpreter

I *(name)* …… declare that:

- I assisted the investigator (*name*) ……. to explain the information in this document

  to (*name of participant*) …….. using the language medium of Afrikaans/Sotho.

- We encouraged him/her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at (*place*) ..... on (*date*) ……2015

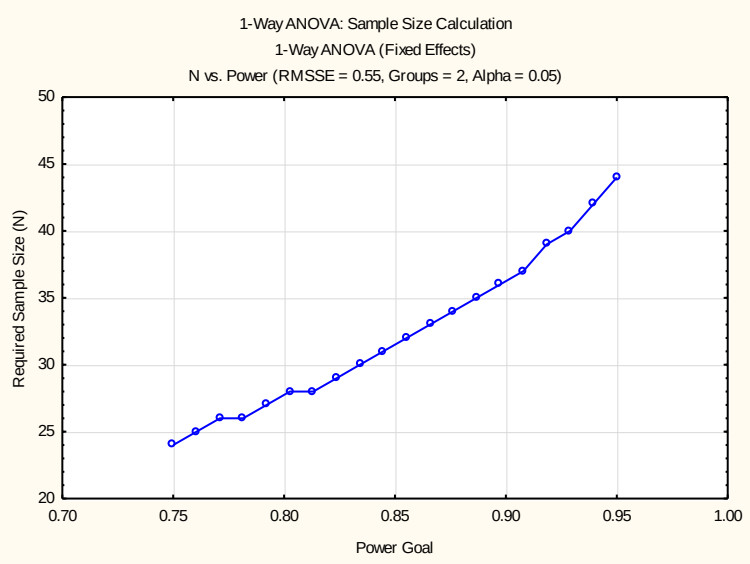
…… ……

Signature of interpreter **Signature of witness**

Appendix C

Sample size calculation

1-Way ANOVA: Sample Size Calculation



Sample Size Calculation ([No active dataset])

	Sample Siz ANOVA, 1-\ Fixed Effec
	Value
Number of Groups	2.000(
RMSSE	0.550(
Noncentrality Parameter (Delta)	3.025(
Type I Error Rate (Alpha)	0.050(
Power Goal	0.900(
Actual Power for Required N	0.902:
Required Sample Size (N)	36.000(

Appendix D

Published Review article

South African Journal of Clinical Nutrition 2017; 30(3):38-48

SAJCN
ISSN 1607-0658 EISSN 2221-1268

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	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.
	2017	**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

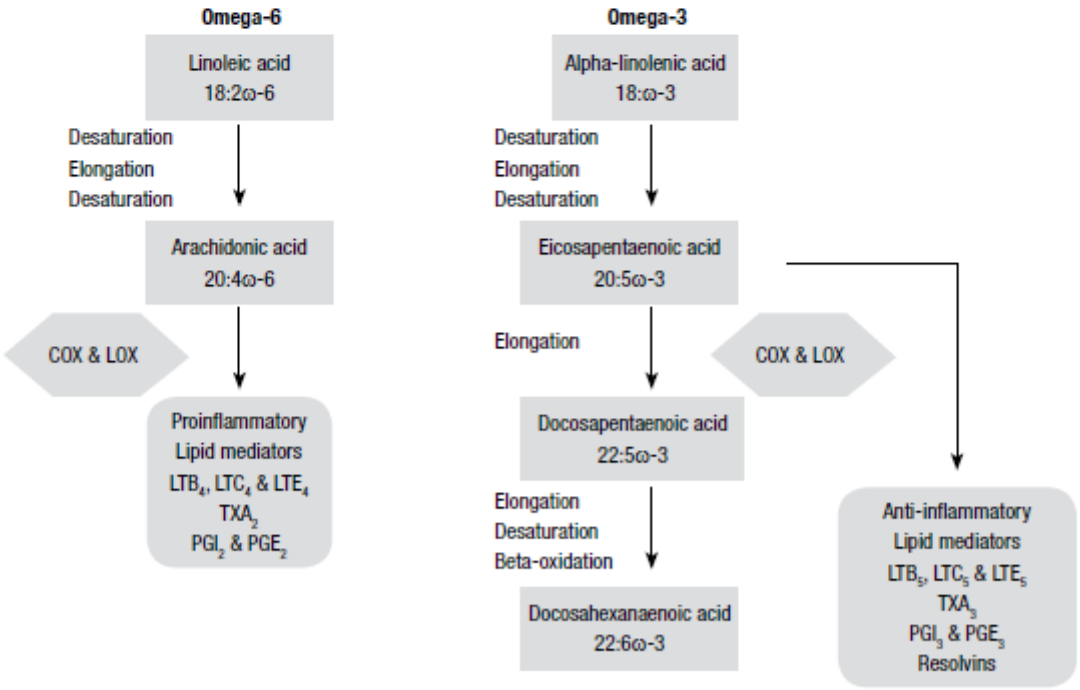


Figure 1: Metabolism of Omega-6 and Omega-3 polyunsaturated fatty acids (adapted from 31-33)
COX – Cyclooxygenase, LOX: Lipoxygenase, TXA2: Thromboxane A2 (platelet aggregator, vasoconstrictor), PGI2: Prostaglandin I2 (vasodilator, antiaggregator), PGE2: Prostaglandin E2 (Immunosuppressor)

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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