Effect of omega-3 fatty acids on the clinical outcomes of mechanically ventilated critically ill patients: a systematic review

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DECLARATION

I, Rehette Greyling, declare that this systematic review is my own work and is submitted in partial fulfilment of the requirements for the degree MSc Dietetics. It has not been submitted to any other institution.

31/05/2018

Signature

Date

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ABSTRACT

Introduction: Mechanical ventilation (MV) is a life-saving strategy associated with serious complications. Early weaning is required to prevent ventilator-associated events (VAE). Previous studies have shown that omega-3 fatty acids (n-3 FA) could reduce the number of days that a critically ill patient is on MV. Many of the conditions indicating the need for MV, as well as some of the complications of prolonged MV, have a strong inflammatory component which could be ameliorated by the anti-inflammatory properties of n-3 FA. Through these mechanisms, the production of anti-inflammatory cytokines is favoured and can contribute to decreased inflammation, which, in turn, may result in improved oxygenation and, ultimately, earlier weaning from MV. This systematic review therefore aimed to critically review published data to determine the effectiveness of n-3 FA on length of ventilation (LOV) as well as other clinical outcomes.

Methods: Electronic searches of MedLine, Scopus, EBSCOhost and ScienceDirect were conducted from 2000 to 2017 in accordance with the PRISMA method. Randomised clinical trials (RCTs) comparing fish oil supplementation in critically ill, mechanically ventilated patients *via* either the enteral or parenteral route were included. Data were pooled and analysed according to the route of feeding. Heterogeneity was assessed visually and by the Chi^2 test with a p-value of less than 0.1 considered significant. This was further quantified by the I^2 test.

Results: A total of eight enteral RCTs (n=1032) and four parenteral RCTs (n=411) met the inclusion criteria for this systematic review. Following statistical analysis, no significant differences were found with regards to LOV in patients receiving parenteral n-3 FA at day 4 (p=0.51, I^2=0%) or day 7 (p=0.54, I^2=0%). There were also no significant differences regarding LOV in patients receiving enteral n-3 FA (p=0.68, I^2=61%). Analysis of available data of PF ratio, intensive care unit length of stay (ICU LOS) and mortality also did not indicate any significant differences in either groups receiving enteral or parenteral n-3 FA when compared to the control groups. The overall risk of bias of the included RCTs was high and the overall quality, as assessed according to GRADE, was very low.

Conclusion: From the available evidence it appears that supplementation with either parenteral or enteral n-3-containing products has no effect on LOV, the ratio of partial pressure of arterial

oxygen to the fraction of inspired oxygen (PF ratio) or mortality outcomes in mechanically ventilated critically ill patients. More high quality, large-scale RCTs, that adequately addressed the issues surrounding risk of bias, are required in order to verify the results of previous studies and provide more reliable evidence that can be translated into practice guidelines.

Key words: Mechanical ventilation, critical illness, Omega-3 fatty acids, clinical outcomes, inflammation

OPSOMMING

Inleiding: Meganiese ventilasie is ‘n lewensreddende strategie wat met ernstige komplikasies geassosieer word. Dit is van groot belang om die pasiënt so gou moontlik van die ventilator af te speen om ventilator- geassosieerde voorvalle te voorkom. Vorige studies het gewys dat die toediening van omega-3 vetsure (n-3 FA) die periode wat ‘n kritieke pasiënt afhanklik is van meganiese ventilasie, kan verminder. Baie toestande wat meganiese ventilasie verlang asook sommige van die komplikasies van verlengde ventilasie het ‘n noemenswaardige inflammatoriese komponent, wat deur die anti-inflammatoriese eienskappe van omega-3 vetsure (n-3 FA) verbeter kan word. Met behulp van hierdie meganisme word die produksie van anti-inflammatoriese sitokiene bevorder, en dit kan bydrae tot verminderde produksie van inflammasie wat op sy beurt weer kan lei tot verbeterde oksigenering en uiteindelik vroeër spening van die ventilator. Die metodiese oorsig se doelwit is om die effek van omega-3 vetsure op die tydperk aan die meganiese ventilator gekoppel, asook ander moontlike kliniese uitkomste te bepaal.

Metodes: Elektroniese soektogte is tussen 2000-2017 op MedLine, Scopus, EBSCOhost en ScienceDirect uitgevoer volgens die “PRISMA” metode. Ewekansige kliniese proewe wat visolie-aanvullings in die kritieke siek, meganiese geventileerde pasiënte via buis- en aarvoeding gebruik is, is ingesluit. Die data is saamgevoeg en geanaliseer volgens die voedingswyses. Heterogeniteit is visueel bepaal, asook deur die Chi^2 toets met ‘n p-waarde van minder as 0.1 wat as beduidend beskou word. Dit is verder gekwantifiseer deur die I^2 toets.

Resultate: In totaal is daar agt enterale (n=1032) en vier parenterale (n=411) ewekansige kliniese toetse in die metodiese oorsig wat aan die insluitingskriteria voldoen, ingesluit. Na die statistiese analise is daar geen noemenswaardige verskil met betrekking tot die tydperk aan ‘n ventilator gekoppel, gevind nie. Hierdie bevinding is van toepassing op pasiënte wat parenterale omega-3 vetsure op dag 4 (p=0.51, I^2=0%) of dag 7 (p=0.54, I^2=0%) ontvang het. Verder was ook geen beduidende verskil m.b.t. meganies geventileerde pasiënte wat enterale omega-3 vetsure (p=0.68, I^2=61%) ontvang het nie. Analise van die beskikbare data m.b.t. die PF- verhouding, tydperk in die intensiewesorgeenheid en mortaliteit het ook geen beduidende verskil in beide die parenterale en enterale voedingswyses, met die toediening van omega -3 vetsure gemaak nie.

Die algehele risiko van vooroordeel m.b.t. die ewekansige kliniese proewe wat geanaliseer is, was hoog en die algehele kwaliteit gebasseer op “GRADE”, was baie laag.

Gevolgtrekking: Volgens die beskikbare bewyse kan die gevolgtrekking gemaak word dat omega-3 vetsuuraanvullings in beide enterale- en parenterale voedingswyses in meganiese geventileerde pasiënte geen effek op die tydperk van ventilasie, PF- verhouding of moraliteit het nie. Meer grootskaalse ewekansige kliniese proewe, wat die probleme rondom die risiko van vooroordeel aanspreek is nodig om die resultate van vorige studies te verifieer en sodoende meer betroubare bewyse te verskaf wat in praktiese riglyne opgeneem kan word.

Sleutelterme: Meganiese ventilasie, kritieke pasiënt, Omega-3 vetsure, kliniese uitkomste, inflammasie.

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LIST OF ABBREVIATIONS

AA	Arachidonic acid
ALA	α-linolenic acid
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
ASPEN	American Society of Parenteral and Enteral Nutrition
CARS	Compensatory anti-inflammatory response syndrome
CCI	Chronic critical illness
CMFs	Chemical mediators of inflammation
CO2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxygenase
CRP	C-reactive protein
CVD	Cardiovascular disease
DHA	Docosahexanoic acid
DM	Diabetes Mellitus
EPA	Eicosapentaenoic acid
ESPEN	European Society of Nutrition and Metabolism
ETT	Endotracheal tube
FA	Fatty acids
GDP	Gross domestic product
GLA	γ-linolenic acid
IBD	Inflammatory bowel disease
ICU	Intensive care unit
IL	Interleukin
IRDS	Idiopathic respiratory distress syndrome

LCPUFA	Long-chain poly-unsaturated fatty acid
LOS	Length of stay
LOV	Length of ventilation
LOX	Lipoxygenase
LT	Leukotrienes
MCT	Medium-chain triglycerides
MOF	Multiple-organ failure
MV	Mechanical ventilation
n-3 FA	Omega-3 fatty acids
n-6 FA	Omega-6 fatty acids
NF-κB	Nuclear-factor kappa B
NIV	Non-invasive ventilation
NS	Nutrition support
PEEP	Positive end-expiratory pressure
PF ratio	Ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen
PGE	Prostaglandins
PICS	Persistent immunosuppression, inflammation and catabolism syndrome
PMV	Prolonged mechanical ventilation
P Plateau	Plateau pressure
PUFA	Poly-unsaturated fatty acid
REE	Resting energy expenditure
ROS	Reactive oxygen species
RQ	Respiratory quotient
SA	South Africa
SA DOH	South African Department of Health
SBT	Spontaneous breathing trial
SCCM	Society of Critical Care Medicine
SD	Standard deviation

SIRS	Systemic inflammatory response syndrome
TNF	Tumour necrosis factor
TRLs	Toll-like receptors
TX	Thromboxanes
VAP	Ventilator-associated pneumonia
VIDD	Ventilator-diaphragmatic dysfunction
VILI	Ventilator-induced lung injury

LIST OF UNITS AND SYMBOLS

α	Alpha
β	Beta
γ	Gamma
κ	Kappa
kg	Kilogram
mg/dl	Milligram per decilitre
ml	Millilitre
mm^3	Cubic millimetre
mmHg	Millimetres Mercury
PCO_2	Partial pressure of carbon dioxide
PO_2	Partial pressure of oxygen
SaO_2	Oxygen saturation
V_T	Tidal volume

CHAPTER 1 INTRODUCTION TO THE MINI-DISSERTATION

1.1 Background

Admission to the Intensive Care Unit (ICU) is predominantly indicated by the need for mechanical ventilation (MV) to support or restore a state of homeostasis (Cairo, 2015:46). This occurs in cases of ventilatory or oxygenation failure and MV is one of the most commonly used interventions in the ICU (Cairo, 2015:46; Chang, 2013:18; Jaber *et al.*, 2011:206; Petrof, 2013:R181). Mechanical ventilation in critically ill patients is considered a life-saving intervention, although it is associated with various serious complications (Jaber *et al.*, 2011:206; Petrof, 2013:R181). Critically ill patients, irrespective of whether MV is necessary, require specialised nutrition support (NS) which has been shown to improve clinical outcomes such as morbidity, mortality and length of ICU stay in this patient population (Dhaliwal *et al.*, 2014:29; Doley *et al.*, 2011:235; McClave *et al.*, 2016:161). Moreover, various nutrients have been individually investigated as adjunctive therapies in the critical care setting. Omega-3 (n-3) fatty acids (FA), a group of polyunsaturated fatty acids (PUFA), have long been studied in various disease conditions, including cardiovascular, lifestyle and inflammatory diseases (Calder, 2015:18S). Eicosanoids, a group of chemical mediators of inflammation (CMFs), are derived from n-3 FAs and include prostanoids and leukotrienes, some of which display more anti-inflammatory effects (Vanek *et al.*, 2012:152).

1.2 Problem statement

Statistics regarding the requirement for and use of MV in South Africa are not readily available. However, a world-wide audit of ICUs published in 2014 indicated that almost half of the patients admitted to ICUs in the African centres required MV (Vincent *et al.*, 2014:380). Also, intensive care facilities in South Africa are extremely limited, especially in the public sector, making cost-effective interventions that will decrease ICU length of stay an essential field of investigation (Hurri, 2016:1). Supplementation with n-3 FAs is relatively inexpensive compared with other medical and pharmacological interventions. If shown to be effective, the use of n-3 FAs can have a positive impact, not only on clinical outcomes, but also on healthcare costs. Omega-3 FA is an essential fatty acid and forms part of basic nutritional requirements. Omega-3 FA may further contribute to improved ventilatory dynamics and earlier weaning from mechanical ventilatory support. Because MV is associated with various complications, aiming for early weaning from MV is desirable as this can contribute to improved clinical outcomes in relation to duration of MV, length of stay and morbidity (Manzanares *et al.*, 2015:167). It stands to reason, therefore, that any interventions that can aid in attaining early weaning from MV should be explored.

Currently, studies conducted in critically ill patients to determine the potential benefits of n-3 FA in various clinical outcomes have shown conflicting results and concrete recommendations are unavailable as the administration of n-3 FA is still debatable (Donoghue *et al.*, 2017:45).

Systematic reviews typically aid in making clinical judgements based on sound evidence-based data (Blackwood *et al.*, 2014:886). This systematic review will contribute to the better understanding of the role of n-3 FA administration in mechanically ventilated patients by taking into consideration relevant research on this topic.

1.3 Research aims and objectives

The aim of this research project was to perform a systematic review of studies investigating n-3 FA administration on clinical outcomes of mechanically ventilated, critically ill patients.

In an attempt to address the research question, the following specific objectives were set:

- To investigate the effect of parenterally administered n-3 FAs on the clinical outcomes of mechanically ventilated, critically ill patients when compared with standard care.
- To investigate the effects of enterally administered n-3 FAs on the clinical outcomes of mechanically ventilated, critically ill patients when compared with standard care.

The specific clinical outcomes included as part of the data extraction process were length of MV, the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (PF ratio), mortality and ICU length of stay. Additionally, safety of administration of n-3 FAs *via* both routes was assessed by reviewing reports of adverse events.

1.4 Layout of this mini-thesis

This introductory chapter serves to provide an overview of the context from in the research question has been set by referring to the necessary supporting background information regarding the topic at hand. Chapter two comprises the full literature review, which provides insight into the theory pertaining to the use of n-3 FAs in the critically ill patient requiring MV and its clinical relevance, based on the available published information. This was done within the framework of the multiple mechanisms of inflammatory responses in this specific patient population.

Chapter three contains the journal article intended for publication in *Clinical Nutrition* and written according to the specific requirements of this journal. A detailed discussion integrating the data from available clinical trials, in-depth analysis of the methodology of the included studies and

available theory is covered in chapter four. Possible confounding factors and recommendations for the design of future clinical trials are also explored in this chapter.

1.5 Contributions of research team members

The following table mentions the members of the research team involved in the compilation of this systematic review and also indicates the contribution of each individual member.

Table Error! No text of specified style in document.**-1 Members of the research team**

Name	Qualification	Professional registration	Role and responsibility
Me R Greyling	BDietetics	DT0031399	MSc Dietetics student Data search, data extraction, statistical analysis and writing of protocol and systematic review as well as writing of the mini-dissertation.
Mrs A Nienaber	MSc Dietetics	DT0034886	Co-Supervisor Provided expert advice on MV, clinical care and n-3 FA. Critically appraised the data extracted and gave support in the writing of the protocol and systematic review.
Dr MJ Lombard	PhD Dietetics	DT0014702	Supervisor Assistance and guidance with data searches and extraction, writing of protocol and systematic review. Critically appraised the data extracted and gave support in the writing of the protocol and systematic review.
Dr C Ricci	PhD Biomedical Statistics	NA	Critically appraised the data extracted and performed the necessary, relevant statistical analyses.

The protocol for the systematic review was approved by the scientific review committee (SRC) of the Centre of Excellence for Nutrition at the North-West University (NWU) and the journal article will be submitted for consideration for publication to the journal *Clinical Nutrition*.

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CHAPTER 2 LITERATURE REVIEW

2.1 Introduction

The Society of Critical Care Medicine (SCCM) proposes a definition of intensive care as the need for invasive and intensive monitoring as well as support of the airway, breathing and circulation (Critical Care Statistics n.d). Critical care practices include resuscitation, diagnosis and provision of appropriate care for acutely ill patients, as well as recognition and management of complications that may arise (Adhikari *et al.*, 2010:1339). Admission to an Intensive Care Unit (ICU) is indicated mainly by the need for mechanical ventilation (MV) to aid in the restoration of homeostasis (Cairo, 2015:46).

Statistics regarding the burden of critical illness, especially in South Africa (SA), are not readily available. Vincent *et al.* (2014) conducted a worldwide audit of ICUs in order to provide much needed data regarding the burden of critical illness across the different continents. The authors reported a global ICU mortality of 16.2% and noted a much higher mortality rate among those ICU patients diagnosed with sepsis (Vincent *et al.*, 2014:380). They also found an inverse relationship between global national income and adjusted risk of in-hospital death (Vincent *et al.*, 2014:380). Only a small fraction of the data collected in this audit was from ICUs located in Africa. An ICU mortality rate of 16.9% across 11 African centres was reported (Vincent *et al.*, 2014:383). Also of note is the fact that, of those patients included from the African centres, 49.6% required mechanical ventilation (MV) (Vincent *et al.*, 2014:380). An earlier local publication reported South African ICU mortality as high as 31.5% (De Beer *et al.*, 2011:6).

The negative impact of critical illness and its complications inevitably contributes to increased healthcare costs which, in turn, affect the gross domestic product (GDP) (Vincent *et al.*, 2014:380). Overall, intensive care services in SA are limited as only 23% of public hospitals have ICU facilities available (Hurri, 2016:1). Therefore, efforts should be made to investigate strategies that could contribute to decreasing the length of ICU stay, including early weaning from MV, in order to optimise the use of this sparse resource.

Nutrition support (NS) in the critical care setting is a vital strategy for improving patient outcomes and there is no shortage of evidence demonstrating the positive correlation between adequate nutritional support and outcomes such as reduced length of MV, length of hospital stay and mortality (Binkowska *et al.*, 2015:206; Dhaliwal *et al.*, 2014:29; Doley *et al.*, 2011:235; McClave *et al.*, 2016:161; Weijs *et al.*, 2012:61). Critical illness is hallmarked by profound and ongoing catabolism related to the metabolic changes brought on by stress-induced inflammatory

processes, which can be attenuated by NS (Muszynski *et al.*, 2016:267). In addition to this, specific nutrients have been investigated for their ability to modulate the metabolic response to stress by enhancing immune function. This aspect of NS, referred to as immunonutrition, includes the nutrients glutamine, arginine, omega-3 fatty acids (n-3 FA), nucleotides and antioxidants (Aqeel *et al.*, 2017:114; Roehl, 2016:27). Many of these nutrients have been studied at various dosages and as a single unit or in combination with each other, yet results have been contradictory and there are more precise guidelines for the administration some of these nutrients than for others (McClave *et al.*, 2016:174; Roehl, 2016:27).

As ongoing inflammatory processes are associated with both critical illness and the effects of MV, it stands to reason that nutrients that display immune modulatory properties can be of great value as part of the effective management of this patient population. The focus of this literature review is on the specific role of n-3 FA in the inflammatory processes associated with MV in critically ill patients.

2.2 Mechanical ventilation in the critically ill patient

During critical illness, the need for MV is directed by the inability of a patient to maintain homeostasis (Cairo, 2015:46). The desired outcome of MV is to achieve normalisation of arterial blood gas levels, as well as acid-base balance (Grossbach *et al.*, 2011:30).

There are two methods of MV, namely invasive and non-invasive MV. Invasive MV involves endotracheal intubation, a high-risk procedure that might result in significant morbidity and mortality as substantial complications occur in up to 40% of all cases (Lapinsky, 2015:258). Although associated with various serious complications, it remains an indispensable strategy in the management of this patient population (Burns *et al.*, 2013:1; Jaber *et al.*, 2011:206; Petrof, 2013:R181). Non-invasive ventilation (NIV) involves the delivery of ventilatory support *via* an oronasal or nasal mask, or by means of a total face mask which is connected to a ventilator, thus eliminating the need for an endotracheal tube (ETT) and reducing the associated risk of micro-aspiration of contaminated secretions (Burns *et al.*, 2013:1; Deem *et al.*, 2016:72).

Prolonged MV (PMV) generally refers to periods of ventilation of more than 14 - 21 days, although definitions differ (Bice & Carson, 2017:251). Patient populations that often require PMV include those presenting with spinal cord injuries, chronic pulmonary conditions and chronic critical illness (CCI) (Doley *et al.*, 2011:232). Studies indicate that PMV is negatively associated with clinical outcomes, including increased rates of mortality related to complications arising from the intervention, as well as higher rates of ventilator-associated pneumonia (VAP) (Blackwood *et al.*,

2011:342). Resource requirements are also significantly higher in patients requiring PMV owing to the increase in length of ICU stay (Bice & Carson, 2017:251; Rose *et al.*, 2015:26).

2.2.1 Indications for mechanical ventilation

Patients who require MV typically present with acute respiratory failure (ARF) caused by trauma, sepsis, pneumonia, congestive cardiac failure or respiratory failure as a result of numerous other conditions, or postoperatively (McConville & Kress, 2012:2233). Clinically, the need for MV is indicated mainly by a pH of less than 7.25, an arterial partial pressure of carbon dioxide (P_aCO_2) of more than 55 mmHg, as well as a dead space to tidal volume ratio (V_D/V_T), each indicator measured in millilitres (ml), of more than 0.6 (Cairo, 2015:47). Table 2-1 lists the clinical conditions causing MV to be indicated.

There are various pulmonary and non-pulmonary conditions that can lead to combinations of dead space ventilation and diffusion defects, as well as ventilatory and oxygenation failure (Cairo, 2015:46; Chang, 2013:18). These conditions can be divided into three main groups: conditions causing depressed respiratory drive, conditions causing excessive ventilatory workload and conditions causing the failure of ventilatory pump, summarised in Table 2-1 (Chang, 2013:18).

Table Error! No text of specified style in document.**-2 Indications for mechanical ventilation (MV) (adapted from Chang (2013:19))**

Mechanism	Clinical condition
Depressed respiratory drive	• Drug overdose • Acute spinal cord injury • Traumatic head injury • Neurological dysfunction, including cerebral vascular accident or hypoxic brain injury • Sleep disorders, including sleep apnoea • Metabolic alkalosis
Excessive ventilatory workload	• Status asthmaticus • Chronic obstructive pulmonary disease (COPD) • Pulmonary embolism • Emphysema • Congenital heart disease • Decreased cardiac output • Peripheral vasodilation • Congestive heart failure • Acute pulmonary oedema • Bronchospasm • Acute lung injury (ALI) • Acute respiratory distress syndrome (ARDS) • Tension pneumothorax • Diaphragmatic hernia • Obesity
Ventilatory pump failure	• Chest trauma • Idiopathic respiratory distress syndrome (IRDS) • Hyperkalaemia • Respiratory muscle fatigue

Abbreviations: ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome; COPD: Chronic obstructive pulmonary disease; IRDS: Idiopathic respiratory distress syndrome

2.2.2 Complications associated with mechanical ventilation

Invasive MV is an indispensable, lifesaving strategy despite the fact that it is associated with various complications (Beitler *et al.*, 2016:633; Burns *et al.*, 2013:1). These complications can be either infectious or non-infectious. Although the incidence might vary, none of these complications is more profound than another as all of them affect patient outcomes negatively. Length of ventilation is associated with increased risk and occurrence of complications and negatively impacts morbidity and mortality, increasing the burden of healthcare costs (Safdar *et al.*, 2016:350). The three main complications associated with MV are ventilator-induced lung injury (VILI), ventilator-induced diaphragmatic dysfunction (VIDD) and ventilator-associated pneumonia (VAP) (Zein *et al.*, 2016:65), which will now be discussed in greater detail.

2.2.2.1 **Ventilator-induced lung injury**

Ventilator-induced lung injury (VILI), an iatrogenic complication of MV, represents a variety of mechanisms involving mechanical forces that either cause lung injury or exacerbate it in cases of pre-existing lung injury (Blackwood *et al.*, 2011:342; Fan *et al.*, 2013:85; Jaber *et al.*, 2011:206; Slutsky, 2015:1107; Wilson & Takata, 2013:175). This complication affects especially those patients with acute respiratory distress syndrome (ARDS) or those who suffer simultaneous insults, including sepsis and trauma (Beitler *et al.*, 2016:634; Wilson & Takata, 2013:175). The mechanical forces involved are stress and strain (Beitler *et al.*, 2016:635; Silva *et al.*, 2015:302). Stress is defined as force per unit of area whereas strain refers to the force exerted along the longitudinal axis, expressed as the ratio between lung volume change and volume at rest (Beitler *et al.*, 2016:635; Fan *et al.*, 2013:86; Silva *et al.*, 2015:302). Ventilator-induced lung injury (VILI) is associated with increased vascular permeability, pulmonary oedema, as well as inflammatory cell infiltration (Slutsky & Ranieri, 2013:2126).

Barotrauma, volutrauma, atelectrauma and biotrauma have been described as the four mechanisms in the pathophysiology of VILI (Beitler *et al.*, 2016:634). Barotrauma signifies lung injury resulting from elevated transpulmonary pressure whereas volutrauma suggests lung injury caused by overdistention due to high volumes (Beitler *et al.*, 2016:635; Slutsky & Ranieri, 2013:2130). The third mechanism, atelectrauma, describes injury caused by cyclical alveolar collapse and reopening due to high shear forces which also effect surfactant function (Beitler *et al.*, 2016:635; Slutsky & Ranieri, 2013:2130).

The inflammatory response triggered by MV is termed biotrauma (Fan *et al.*, 2013:86). Biotrauma is caused by direct injury to the lung cells as well as conversion of the injury caused by the mechanical forces that act as a trigger for inflammatory pathways (Fan *et al.*, 2013:86; Slutsky &

Ranieri, 2013:2130). Mediators released as a result of activation of the immune response, including tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6), can cause further damage to lung tissue (Slutsky & Ranieri, 2013:2128). As VILI is associated with increased vascular permeability, there is a high possibility of translocation of inflammatory mediators, as well as bacteria, into systemic circulation, which could lead to multiple-organ dysfunction and thus negatively impact on clinical outcomes (Beitler *et al.*, 2016:637; Slutsky & Ranieri, 2013:2128). Minimisation of the detrimental effects of VILI includes not only attempts to wean the patient early, but also lung-protective ventilation methods incorporating the use of low tidal volumes, higher positive end-expiratory pressure (PEEP) and lung recruitment tactics (Slutsky & Ranieri, 2013:2131).

2.2.2.2 **Ventilator-induced diaphragmatic dysfunction**

Contributing to failure to wean from MV is ventilator-induced diaphragmatic dysfunction (VIDD), a condition caused by structural injury and atrophy of diaphragmatic muscle fibres coupled with a reduction of diaphragmatic force-generating capacity (Jaber *et al.*, 2011:206). Patients presenting with diaphragmatic dysfunction have been known to have a worsened prognosis as well as higher rates of mortality (Petrof, 2013:R181). It has been demonstrated that significant diaphragmatic atrophy already occurs in patients on full MV after just 18 to 24 hours (Powers *et al.*, 2013:R466). Ventilator-induced diaphragmatic dysfunction (VIDD) occurs in cases of both full and partial MV, the only difference being the rate of atrophy, which is understandably faster during full MV (Powers *et al.*, 2013:R466). There is a direct correlation between length of MV and muscular atrophy, the amount of diaphragmatic thickness lost being, on average, 6% per day (Powers *et al.*, 2013:R466).

The pathophysiology of VIDD involves changes of both the structure and the biochemistry in the diaphragm of ventilated patients (Jaber *et al.*, 2011:208). Mechanical ventilation (MV) increases the rate of proteolysis within the diaphragm, which alters the structure by causing atrophy of diaphragmatic muscle fibres. Biochemical changes also lead to the activation of protease, which, in turn, causes muscular atrophy, negatively impacting on clinical outcomes (Powers *et al.*, 2013:R468).

2.2.2.3 **Ventilator-associated pneumonia**

During endotracheal intubation, the risk of micro-aspiration of contaminated secretions is high. The resulting infection that commonly presents within 48 to 72 hours post-intubation is referred to as ventilator-associated pneumonia (VAP) (Charles *et al.*, 2014:334; Deem *et al.*, 2016:72; Kalanuria *et al.*, 2014:208; Keyt *et al.*, 2014:814; Safdar *et al.*, 2016:350). Classified as a hospital-

acquired infection, VAP has a reported incidence of 13 – 51 per 1000 ventilator days; this can differ, however, depending on the specific setting and patient population together with the definition and criteria used for diagnosis (Charles *et al.*, 2014:334; Kalanuria *et al.*, 2014:208).

The risk of developing VAP is directly associated with duration of MV although it is higher during the first five days following intubation (Keyt *et al*., 2014:815). Therefore, early weaning from MV is key to reducing the risk of VAP (Kalanuria *et al*., 2014:213; Keyt *et al.*, 2014:815). In addition to early weaning, other necessary strategies include non-invasive ventilation, weaning trials, head-of-bed elevation (semi-recumbent positioning) as well as early tracheostomy (Kalanuria *et al*., 2014:213; Keyt *et al*., 2014:815).

2.2.3 Weaning from mechanical ventilation

Weaning from MV refers to the process of steady withdrawal of MV and simultaneous recommencement of spontaneous breathing (BouAkl *et al.*, 2012:42; Zein *et al.*, 2016:65). In cases of ARF, where gradual weaning is not necessary and patients easily resume spontaneous breathing, the term “liberation” from MV is more appropriate (Amri *et al.*, 2016:1; McConville & Kress, 2012:2233). Investigations have shown that prolonged weaning from MV, defined as weaning efforts that extend over more than seven days, is an independent predictor of discharge from ICU, as well as of one-year mortality (Amri *et al.*, 2016:1; BouAkl *et al.*, 2012:42). In the absence of adequate assessment of readiness for weaning, patients who fail extubation present with significant clinical deterioration following reintubation (BouAkl *et al.*, 2012:42).

The first step to assessing readiness to wean from MV includes resolution of the event that caused respiratory failure (BouAkl *et al.*, 2012:43). Factors that are considered when assessing readiness to wean include subjective as well as objective indicators such as haemodynamic stability and ventilatory dynamics (McConville & Kress, 2012:2233). In many ICUs, weaning protocols are used that commonly consist of three sections: a list of objective criteria to evaluate readiness to wean, guidelines for reducing ventilatory support or for testing readiness and, lastly, a list of criteria for extubation (BouAkl *et al.*, 2012:44; McConville & Kress, 2012:2233). Readiness can be tested directly by means of a spontaneous breathing trial (SBT), which entails assessing breathing ability with minimal ventilatory support (BouAkl *et al.*, 2012:44). Failure to wean can be related to respiratory factors or multi-organ dysfunction, amongst others, and has been shown to be an independent predictor of both ICU discharge and mortality at one year (BouAkl *et al.*, 2012:42).

2.3 The immune response in mechanically ventilated, critically ill patients

The activation of the immune system is pivotal to restore homeostasis following injury or in the presence of infection (Binkowska *et al.*, 2015:207). However, persistent and excessive activation of the immune system, which includes both pro- and anti-inflammatory responses, can trigger immune dysfunction which may lead to various adverse clinical outcomes and worsening of disease progression (Binkowska *et al.*, 2015:207). In fact, inflammatory status is directly related to the prognosis of the critically ill patient (Molfino *et al.*, 2017:1). These inflammatory processes and clinical consequences are depicted in Figure 2-1. Both critical illness and sepsis are characterised by inflammation and immune dysfunction (Han & Mallampalli, 2015:855; Manzanares *et al.*, 2015:174). In addition, as discussed above, the invasive procedure of MV also results in tissue injury and consequently stimulates inflammatory processes (Fan *et al.*, 2013:86).

The initial immune response is activated at the primary site of injury or insult and involves mainly the cells of the non-specific, innate immune system (Binkowska *et al.*, 2015:207). The function of this early pro-inflammatory response is to restore physiological homeostasis and is referred to as the systemic inflammatory response syndrome (SIRS) (Binkowska *et al.*, 2015:207). This is counteracted by an anti-inflammatory response, termed the compensatory anti-inflammatory response syndrome (CARS), and involves anti-inflammatory mediators of the adaptive immune system (Binkowska *et al.*, 2015:206; Moore *et al.*, 2017:122S). Excessive and prolonged SIRS can lead to early multiple-organ failure (MOF) as a consequence of extensive tissue and organ damage that is directly related to the inflammatory response (Binkowska *et al.*, 2015:207; Calder, 2013:654; Keel & Trentz, 2005:691; Rangel-Huerta *et al.*, 2012:S159). The immune response, as discussed above, is depicted in Figure 2-1.

In cases where homeostasis is not achieved and immunological dysfunction continues for more than 14 days, patients are considered to have entered a phase referred to as chronic critical illness (CCI), a diagnosis conditional to the presence of organ failure (Rosenthal *et al.*, 2017:54). Traditionally, the focus was primarily on SIRS and CARS, but more recently, the concept of persistent immunosuppression, inflammation and catabolism syndrome (PICS) has been introduced (Moore *et al.*, 2017:121S). This occurrence, also considered in some ways to be a chronic form of MOF, involves prolonged inflammation and catabolism (Moore *et al.*, 2017:121S). About 30% to 50% of patients with CCI develop PICS (Moore *et al.*, 2017:121S; Rosenthal & Moore, 2015:4; Rosenthal *et al.*, 2017:55). These patients typically present with ongoing or recurrent nosocomial infections and severe loss of lean body mass (Moore *et al.*, 2017:121S; Rosenthal *et al.*, 2017:55). Along with these clinical signs, patients most often also have poor wound healing and usually require PMV (Rosenthal *et al.*, 2017:55). In this case, NS is essential

and its benefits are mainly reflected in terms of its positive effect on nosocomial infections (Moore *et al.*, 2017:121S). Unfortunately, adequate NS has not been shown to affect or prevent the intensity of ongoing catabolism (Moore *et al.*, 2017:121S).

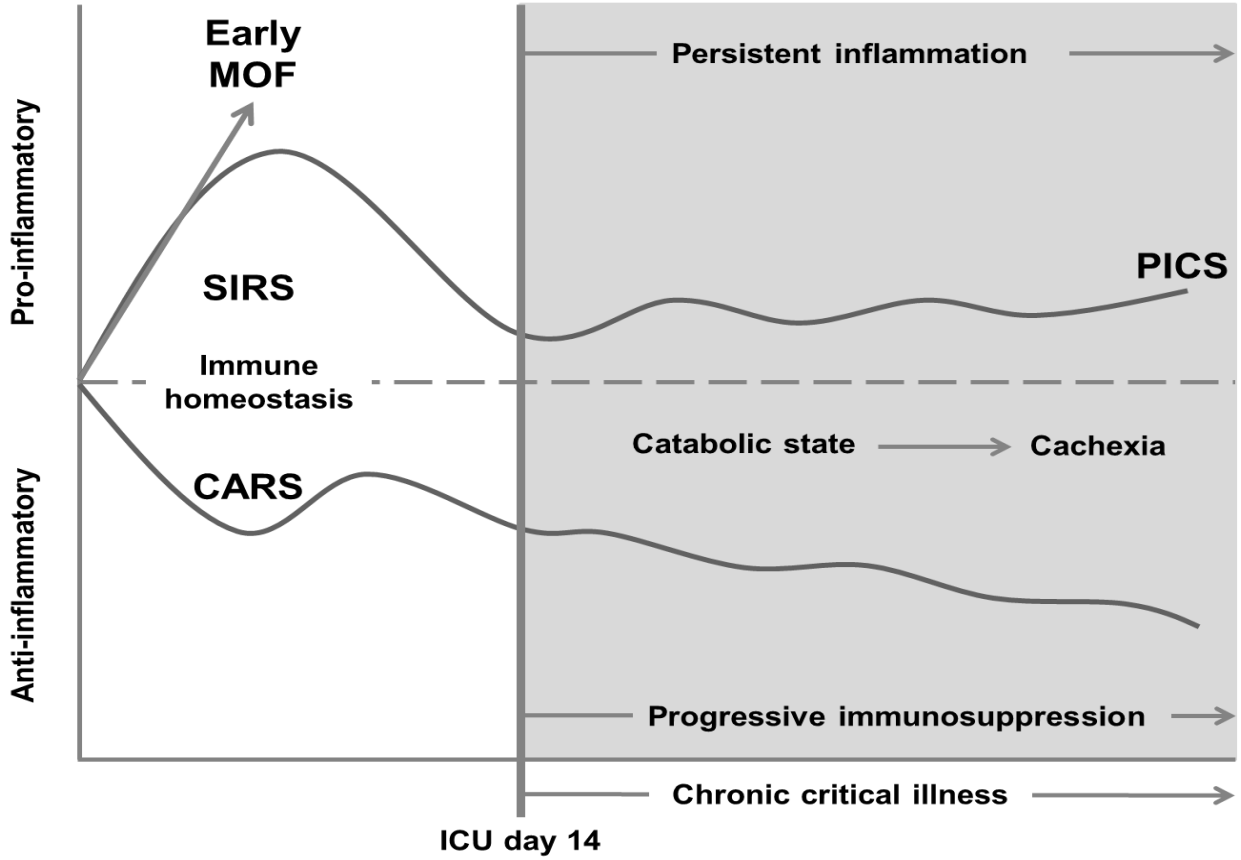

Figure Error! No text of specified style in document.**-1 Diagrammatic representation of the immune response in critical illness (Adapted from Rosenthal *et al.* 2017)**

Toll-like receptors (TLRs) on phagocytes recognise pathogens in addition to endogenous signals from damaged or stressed cells following organ and soft tissue injury, which leads to the activation of the innate immune system (Lenz *et al.*, 2007:1338; Surbatovic *et al.*, 2013:2). This activation takes place irrespective of whether the stimulus is infectious or non-infectious as, for example, in cases of tissue damage (Surbatovic *et al.*, 2013:1). Immune responses might be further amplified by secondary hits, which include bacterial infection, ischaemia/reperfusion injury and stress caused by surgical interventions (Lenz *et al.*, 2007:1338). This is referred to as the multiple-hit hypothesis (Lenz *et al.*, 2007:1338). Following activation of the immune system by TRLs, a series of intracellular events eventually leads to the release of various cytokines (Surbatovic *et al.*, 2013:2). The characteristics of an inflammatory response differ in different organs and within the bloodstream and these characteristics are determined by factors such as pathogen virulence and co-morbidities (Surbatovic *et al.*, 2013:2).

Inflammation is hallmarked by the production of chemical mediators of inflammation (CMFs), which include C-reactive protein (CRP), cytokines, chemokines and lipid mediators (Martin & Stapleton, 2010:531,533). Lipid mediators, produced from fatty acid components of cellular membranes, are one of eight groups of CMFs and include eicosanoids, docosanoids and platelet-activating factors (Martin & Stapleton, 2010:533; Rangel-Huerta *et al.*, 2012:S159). Eicosanoids are considered essential regulators and mediators of inflammation (Calder, 2013:648).

One of the common conditions that require patients to be mechanically ventilated is acute respiratory distress syndrome (ARDS), a condition that has a pertinent inflammatory aspect (Han & Mallampalli, 2015:855). Patients diagnosed with ARDS present with elevated levels of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6 and IL-8, within the lung tissue (in samples of bronchoalveolar lavage fluid), as well as in circulating plasma, indicating that ARDS is a systemic inflammatory condition involving the lungs and other organs (Han & Mallampalli, 2015:856; Martin & Stapleton, 2010:532). Critically ill patients with sepsis, who are also often ventilated, may possibly also benefit from interventions that address the inflammatory aspects of both critical illness and sepsis (Lu *et al.*, 2017:59). Sepsis is caused by an inappropriate and extensive host response to infection that causes fatal organ damage and typically results in a high mortality rate (Binkowska *et al.*, 2015:206; Lee *et al.*, 2016:1; Lu *et al.*, 2017:58). Hence, treatment strategies focusing on anti-inflammatory mechanisms can be of great benefit in these specific critically ill patient populations. Because available trials conducted among septic patients are generally of low quality, very few concrete recommendations can be made (Lu *et al.*, 2017:67).

2.4 Nutrition support in the mechanically ventilated, critically ill patient

Nutritional support (NS) in the critical care setting and specifically in MV patients is a vital strategy for improving patient outcomes, as it forms an integral part of the effective management of the critically ill, ventilated patient (McClave *et al.*, 2016:161). It is important not only to sustain the immune response during critical illness, but also to maintain adequate muscle mass. There is no shortage of evidence demonstrating the positive correlation between adequate nutrition support and improved patient outcomes, including reduced duration of MV and length of hospital stay, as well as reduction in mortality (Binkowska *et al.*, 2015:206; Dhaliwal *et al.*, 2014:29; Doley *et al.*, 2011:235; McClave *et al.*, 2016:161; Weijs *et al.*, 2012:61). The importance of nutrition in this setting has become so apparent that it is now more commonly referred to as nutrition therapy instead of simply being considered an adjunctive support strategy (McClave *et al.*, 2016:161).

In addition to its positive impact on mortality, optimal NS, often defined as the early provision of sufficient energy and protein, has been known to reduce the incidence of infectious complications (Binkowska *et al.*, 2015:206; Weijs *et al.*, 2012:61). Considering the metabolic changes that cause

drastically altered nutritional needs during critical illness, these patients are at an even higher risk of developing malnutrition, especially in the absence of appropriate NS (Ridley *et al.*, 2015:565) (Afifi *et al.*, 2013:203). It has been well documented that malnutrition negatively impacts clinical outcomes of the critically ill and, owing to the resulting weakened diaphragmatic muscles, also complicates weaning from MV (Doley *et al.*, 2011:234; Lee *et al.*, 2016:1; Rehal *et al.*, 2016:138; Ridley *et al.*, 2015:565). Diaphragmatic weakness, ICU-acquired weakness and deteriorating nutritional status may result in a multitude of complications that have negative effects on clinical outcomes. It has been found that insufficient provision of energy plays a significant role in the occurrence of complications, including infectious complications, and a considerable increase in mortality rates. Conversely, overfeeding may result in excessive CO_2 production, which can also complicate weaning from MV (Doley *et al.*, 2011:235; Preiser *et al.*, 2015:38).

Malnutrition in hospitalised patients, a condition referring to both under- and overnutrition, is a well-documented, global phenomenon (Ridley *et al.*, 2015:565; Tappenden *et al.*, 2013:1219). In developed countries, it is estimated that about a third of patients are admitted to hospital with pre-existing malnutrition, specifically undernutrition, and that about a third of patients, who were not malnourished on admission, develop malnutrition during their hospital stay (Tappenden *et al.*, 2013:1220). In the South African context, even though the data available is limited, prevalence of hospital malnutrition has been reported to be as high as 60%, with a recent study indicating a prevalence as high as 69.8% (Blaauw *et al.*, 2017:S251; Blanckenberg, 2012:4).

Despite the realisation that NS is a critical part of the management of a critically ill patient and despite a great deal of research being focused on what is adequate for a critically ill patient, ICU patients generally remain inadequately fed (Weijs *et al.*, 2012:60; Weijs & Wischmeyer, 2013:194). Furthermore, current guidelines regarding the adequate amounts of various nutrients, together with appropriate timing of NS, are conflicting (Weijs *et al.*, 2012:60; Weijs & Wischmeyer, 2013:194). Currently, research conducted in this area is more focused on protein provision and it has been repeatedly shown that, despite attempts at providing optimal NS, protein targets are still not being met (Veldsman *et al.*, 2016:987). A recent local study has shown inadequate protein delivery, specifically in ICU patients, which corresponds to international studies showing similar findings and again highlighting the discrepancies faced with regard to current recommendations and clinical practice (Veldsman *et al.*, 2016:987).

Previously, nutrition support in critically ill patients was aimed mainly at providing only the necessary macronutrients to uphold basic physiological functions (Weijs & Wischmeyer, 2013:194). However, NS does extend beyond the adequate provision of macronutrients. Immunonutrition is an area of NS that focuses on exploring the possible benefit of those nutrients

that are capable of modulating immune function, which include glutamine, arginine, antioxidant micronutrients and n-3 FAs (Aqeel *et al.*, 2017:114; Roehl, 2016:27). Over time, these nutrients have been added to commercial enteral and parenteral products based on available studies indicating possible benefits in various patient populations (Roehl, 2016:27).

2.5 Role of omega-3 fatty acids in the critically ill patient

2.5.1 Biological pathways and physiological functions of omega-3 fatty acids

Fundamentally, fatty acids (FAs) play a role in metabolism as their oxidation provides a source of energy (Calder, 2015:19S). Fatty acids (FAs) also have a functional role as essential components of the phospholipid membrane and are involved in various regulatory functions, as they act as precursors for the production of inflammatory lipid mediators (Calder, 2015:19S; Martin & Stapleton, 2010:533). Fatty Acids (FAs) are classified firstly, according to the number of carbon atoms and secondly, by the number of double bonds that the FA chain contains (Calder, 2010:566; Vanek *et al.*, 2012:150). Polyunsaturated fatty acids (PUFAs) are fatty acids that contain two or more double bonds in the hydrocarbon chain (Calder, 2010:565-567; Vanek *et al.*, 2012:150). There are three main long-chain PUFA (LCPUFA) series, namely omega-3, omega-6 and omega-9 LCPUFAs (Vanek *et al.*, 2012:150).

Omega-3 fatty acids (n-3 FA) are LCPUFAs ranging from between 18 to 22 carbon atoms in length, with the first of multiple double bonds located on the third carbon atom relative to the methyl group, whereas n-6 and n-9 have the first double bond on the sixth and the ninth carbon respectively (Calder, 2010:566; Martin & Stapleton, 2010:532; Vanek *et al.*, 2012:150). These PUFAs form essential structural and functional components of phospholipids in cellular membranes (Calder, 2013:651).

There are three types of FA in the n-3 FA series: α-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA), as depicted in Figure 2-2 (Calder, 2010:566; Martin & Stapleton, 2010:532; Vanek *et al.*, 2012:152). As humans are unable to synthesise n-3 FAs *de novo,* these FAs are considered essential and should be included in the daily diet (Calder, 2010:566; Martin & Stapleton, 2010:532). The above-mentioned essential FAs all have different functions in the human body. For example, DHA has crucial structural and functional roles within the brain and eyes and both EPA and DHA have well known roles related specifically to their favourable cellular and metabolic effects on risk profiles in cases of inflammatory conditions or cardiovascular disease (CVD) (Calder, 2015:26S). Sources of dietary n-3 FAs include soybean, canola, flaxseed and fish oil, the latter being the source highest in EPA and DHA (Martin & Stapleton, 2010:532). Although n-3 FA cannot be synthesised in the human body, enzymatic

desaturation and elongation of ALA to EPA and DHA are possible, as also demonstrated in Figure 2 (Calder, 2010:566; Martin & Stapleton, 2010:532).

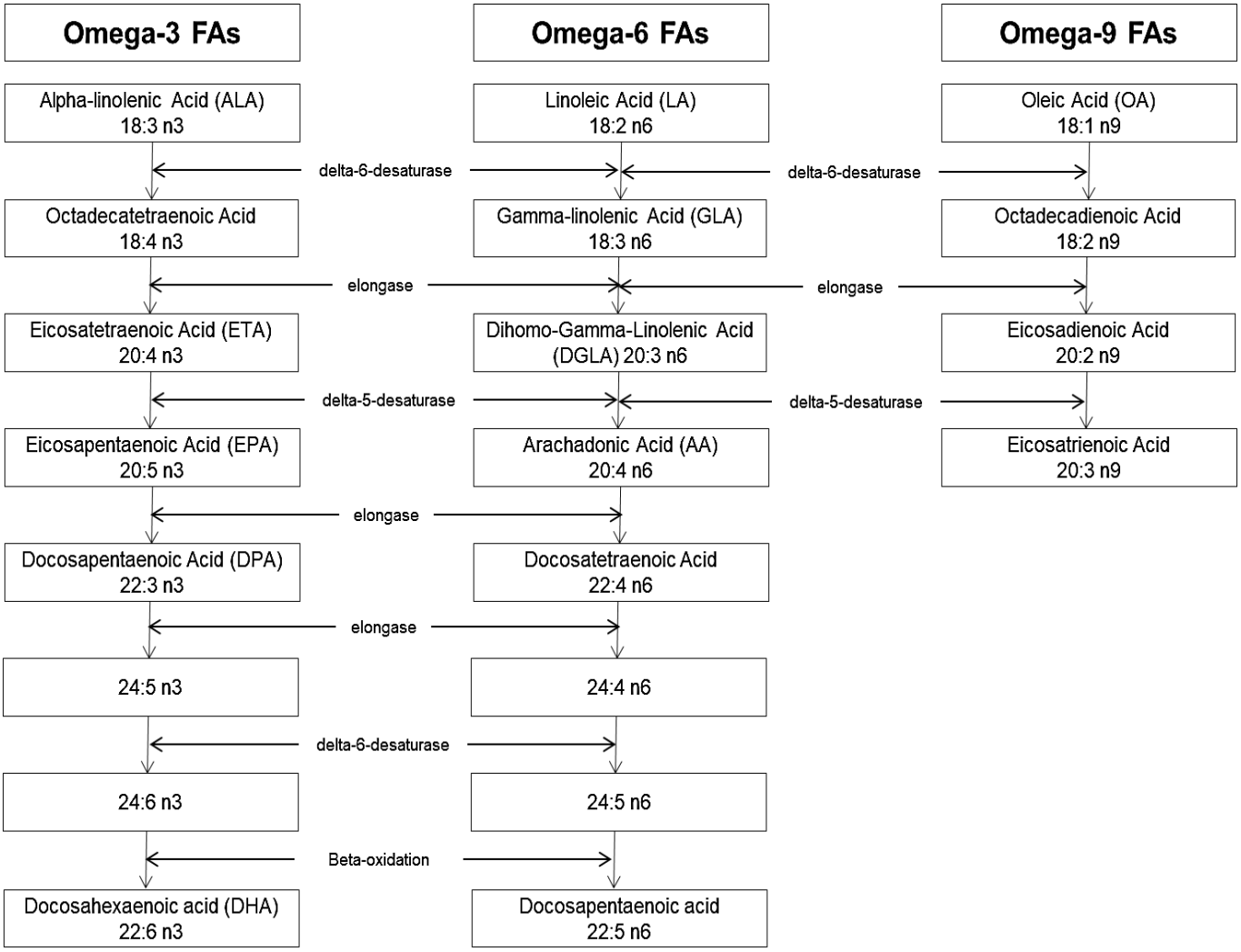

Figure Error! No text of specified style in document.**-2 Pathway of n3 and n6 FA conversion (Adapted from Vanek *et al.*)**

Linoleic acid, an essential n-6 FA, can be metabolised in human cells by a complex pathway (Calder, 2010:566). Linoleic acid is converted to γ-linolenic acid (GLA) *via* a series of enzymes and is eventually converted to arachidonic acid (AA), a precursor of eicosanoids that are considered to be more pro-inflammatory (Calder, 2010:566; Calder, 2013:647; Martin & Stapleton, 2010:533). The production of eicosanoids from AA and EPA is illustrated in Figure 2-3

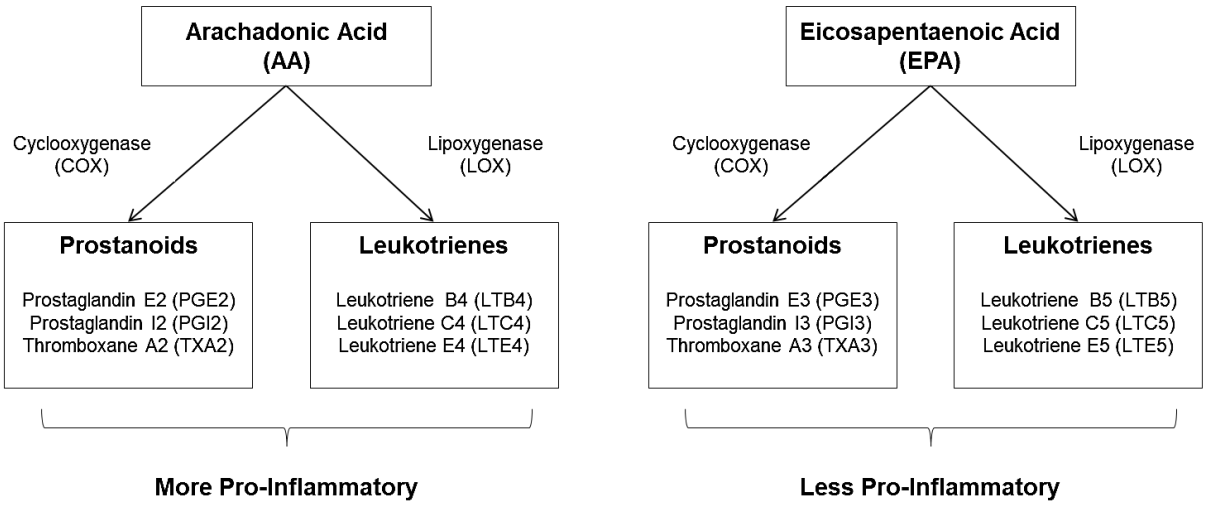

Figure Error! No text of specified style in document.**-3 Illustration of the production of eicosanoids from AA and EPA (Adapted from Vanek *et al.*)**

Alpha-linolenic acid (ALA), an essential 18-carbon n-3 FA, is converted enzymatically to EPA, which can then be converted to DHA *via* further enzymatic reactions as well as oxidation (Calder, 2010:566; Calder, 2013:647; Martin & Stapleton, 2010:533). The same series of enzymes are used for both the conversion of ALA to EPA and for the conversion of linoleic acid to AA (Calder, 2013:646). Because linolenic acid is more prevalent in the typical human diet, this is the pathway mostly prioritised (Calder, 2013:646). Eicosapentanoic acid (EPA) is also converted to prostanoids *via* the enzyme cycloogygenase (COX) and to leukotrienes by the enzyme lipoxygenase (LOX), the latter of which is considered to display fewer pro-inflammatory properties (Figure 2-3) (Martin & Stapleton, 2010:532; Vanek *et al.*, 2012:152). This process is also in competition with the conversion of AA by COX and LOX into more pro-inflammatory prostanoids and leukotrienes (Vanek *et al.*, 2012:150). Therefore, if higher amounts of EPA are available, the production of more favourable eicosanoids is likely.

The role of n-3 FA in various chronic health conditions such as cardiovascular disease (CVD), Diabetes Mellitus (DM) and inflammatory conditions such as arthritis has been extensively investigated (Calder, 2015:27S). There is also evidence of possible benefits in diseases, including inflammatory bowel disease (IBD) and asthma (Calder, 2013:653). Based on the positive results found regarding the use of specific fatty acids in these disease conditions, it is reasonable to hypothesise that, as n-3 FA influences inflammation, its application might stretch much further than chronic diseases and can possibly be of benefit in patient populations with acute inflammatory responses, such as in critically ill patients. This possible application is further discussed in the section below.

2.5.2 The role of omega-3 fatty acids in the inflammatory and immune response

Functionally, as fatty acids are structural components of phospholipid membranes, modification of the membrane can affect the inflammatory response in the presence of increased amounts of EPA and DHA (Calder, 2013:651; Martin & Stapleton, 2010:533). There are a few mechanisms by which n-3 FAs are thought to influence the inflammatory response, including replacement of AA on the phospholipid membrane, increasing production of more anti-inflammatory lipid mediators and affecting membrane fluidity (Calder, 2013:648; Martin & Stapleton, 2010:533).

2.5.2.1 **Influences of n-3 FA on the phospholipid membrane**

As the availability of EPA and DHA increases, AA is replaced in the phospholipid membrane of inflammatory cells, therefore limiting the production of pro-inflammatory eicosanoids such as IL-6, IL-1β and TNF-α (Calder, 2013:648,651; Martin & Stapleton, 2010:533). Eicosapentanoic acid (EPA) also has an additional function of replacing AA (Martin & Stapleton, 2010:533). In the presence of EPA, the metabolism of free AA into particularly inflammatory eicosanoids is inhibited (Martin & Stapleton, 2010:533).

Another prominent effect of n-3 FAs on inflammation is related to the ability of these FAs to alter membrane fluidity (Martin & Stapleton, 2010:533). In turn, the activity of enzymes, receptors and transporters bound to the membrane is disrupted (Martin & Stapleton, 2010:533). The resolution of the inflammatory process does not involve only the absence of inflammatory signals (Martin & Stapleton, 2010:533). Furthermore, the resulting decrease in the T-cell reactivity caused by changes in membrane fluidity could aid in the resolution of the inflammatory process as IL-2 production is decreased (Martin & Stapleton, 2010:533).

2.5.2.2 **Influences on the production of lipid mediators and gene expression**

The lipid mediators, termed resolvins and protectins, are also derived from EPA and DHA. These mediators have been shown to actively resolve inflammation and have a role in repair of tissue in addition to their anti-inflammatory effects, such as the prevention of the infiltration of neutrophils into inflamed sites (Calder, 2013:650; Martin & Stapleton, 2010:533).

Furthermore, EPA and DHA may also affect inflammatory gene expression by the inhibition of nuclear factor kappa B (NF-κB) (Martin & Stapleton, 2010:533). Nuclear factor κB (NF-κB) is a transcription factor that is not only involved in the upregulation of inflammatory molecule production, including pro-inflammatory cytokines, but also plays a role in the reduction of adhesion molecule expression (Martin & Stapleton, 2010:533). This specific transcription factor has been

shown to play a role in development of VIDD in patients on MV as the NF-κB signalling pathway causes skeletal muscle proteolysis (Smuder *et al.*, 2012:927). As PMV is a prevalent problem, the application of this mechanism can be useful in aiding early weaning from MV (Smuder *et al.*, 2012:927). The increased availability of EPA and DHA in the membrane also leads to an increase in the production of endocannabinoids, which can be defined as complex eicosanoids that also have anti-inflammatory properties (Calder, 2013:650).

2.5.2.3 **Additional mechanisms**

There are additional mechanisms by which EPA and DHA influence inflammation, including decreasing leucocyte chemotaxis, as well as decreasing the expression of intercellular adhesion molecules, the latter of which reduces the adhesive interaction between monocytes and endothelial cells (Calder, 2013:648).

2.5.3 The administration of omega-3 fatty acids as part of nutritional support in the critical care setting

2.5.3.1 **General functions of fat emulsions in artificial nutrition**

Lipid emulsions in artificial nutrition products have various functions. As a basic function, lipids provide a dense source of energy which is necessary to attempt to curb the negative effects of energy deficit in critically ill patients (Manzanares *et al.*, 2015:167; Weijs & Wischmeyer, 2013:194). In the mechanically ventilated patient, distributing total energy required by providing a higher amount of fat might result in a lower respiratory quotient (RQ) (Doley *et al.*, 2011:235). This indicates a decreased production of carbon dioxide (CO_2), as carbohydrate availability is restricted and the production of CO_2 therefore limited, which may assist in weaning from MV (Doley *et al.*, 2011:235). The premise for the addition of n-3 FA, specifically, stems from the biochemical effects of these FAs on the inflammatory response, as discussed in the sections above.

2.5.3.2 **Omega 3 in parenteral nutrition**

Classically, parenteral lipid emulsions consisted mainly of soybean oil, a source rich in the essential n-6 FA, linoleic acid, and which has an n-6 to n-3 ratio of 7:1 (Abbasoglu *et al.*, 2017:2; Calder, 2010:566; Manzanares *et al.*, 2015:167). Although clinical trials have found conflicting results, there is evidence to suggest that these soybean-based lipid emulsions might be pro-inflammatory (Calder, 2010:566; Martin & Stapleton, 2010:533). Therefore, various strategies have been proposed in an effort to reduce the total content of n-6 FA in parenteral lipid emulsions (Calder, 2010:566; Manzanares *et al.*, 2015:167). Such strategies include the dilution or partial

replacement of soybean oil emulsion (Calder, 2010:566). The method of dilution usually includes the use of medium-chain triglycerides (MCT), which still results in a n-6:n-3 of 7:1 (Abbasoglu *et al.*, 2017:2; Calder, 2010:566). Olive oil has also been used in conjunction with soybean oil, with the only commercially available product having an n-6 to n-3 ratio of 9:1 (Abbasoglu *et al.*, 2017:2; Calder, 2010:566). The second strategy of partial replacement entails the use of fish oil (Calder, 2010:566; Manzanares *et al.*, 2015:167). These fish oil-containing lipid emulsions have n-6:n-3 ratios ranging from 2.5:1 to 2.7:1, which is thought to display more anti-inflammatory characteristics (Abbasoglu *et al.*, 2017:2).

The anti-inflammatory effects of n-3 FA are dose dependent (Abbasoglu *et al.*, 2017:1). Previous studies which were aimed at evaluating the effect of parenteral n-3 FA supplementation on clinical outcomes of critically ill and surgical patients showed positive effects at doses of between 0.05g/kg/day and 0.15g/kg/day of fish oil (Calder, 2010:568). These were given either in the form of a pure fish oil emulsion or as part of a mixed-lipid emulsion (Calder, 2010:567). More recently, a review by Abbasoglu *et al.* (2017) reported on studies that used various amounts of fish oil to determine the effect on several different clinical outcomes (Abbasoglu *et al.*, 2017:9). The majority of these studies used dosages above 0.05g/kg/day of fish oil (Abbasoglu *et al.*, 2017:9). The authors found that the use of n-3 FA does not significantly improve clinical outcomes, including mortality and length of stay in ICU, despite evidence of a beneficial effect on inflammatory markers (Abbasoglu *et al.*, 2017:11).

2.5.3.3 **Omega-3 in enteral nutrition**

Adding fish oil to artificial nutrition products increases the amount of biologically active EPA and DHA available for production of anti-inflammatory mediators, a process which is then not solely reliant on the conversion of ALA. This, coupled with the resulting reduction of linoleic acid in the lipid emulsion might result in improved cellular and tissue function (Calder, 2010:567). Most of the available studies evaluating the effect of enteral n-3 supplementation have used complete enteral feeds that contain fish oil. However, these products also contain other elements that can alter the inflammatory response, including antioxidant micronutrients, arginine and borage oil, the latter being a source of GLA (Calder, 2010:569). After enzymatic conversion of GLA to Dihomo-GLA, conversion to AA is the next step in the metabolic pathway (Martin & Stapleton, 2010:533). Despite this, with mechanisms not fully understood, Dihomo-GLA reduces the availability of AA, thereby limiting the amount of AA available for the synthesis of pro-inflammatory AA-derived eicosanoids (Martin & Stapleton, 2010:533). Dihomo-GLA itself is converted to prostaglandin E_1, an anti-inflammatory eicosanoid, and seems to have an enhancing effect on the immune response (Martin & Stapleton, 2010:533). Therefore, it is difficult to attribute any positive results purely to

the effect of n-3 FA. As is the case with PN, the required dosage is not clear. Studies that have shown positive effects on clinical outcomes have used dosages of between 4.5 – 5.3g of EPA and 2.2 - 4.3g DHA per day with a ratio of n-3:n-6 of about 1.85:1 (Grau-Carmona *et al.*, 2011:580; Pontes-Arruda *et al.*, 2006:2327).

2.5.3.4 **Available guidelines on the use of n-3 FAs in critically ill patients**

The effect of n-3 FA supplementation has been investigated in a fairly diverse population of critically ill patients, including patients with sepsis and severe acute pancreatitis (SAP), as well as medical ICU patients (Manzanares *et al.*, 2015:170). Despite the amount of research available, clear guidelines regarding the use of n-3 FA in the ICU are still lacking. This can be attributed mostly to the lack of high-quality trials (Abbasoglu *et al.*, 2017:2). International and national guidelines currently available on the use of n-3 FA in the critically ill population are summarised in Table 2-2.

Table Error! No text of specified style in document.**-2 Guidelines for the use of n-3 FA in critically ill patients**

Society	**Year**	**Recommendations:** **Enteral**	**Recommendations:** **Parenteral**
The European Society of Nutrition and Metabolism (ESPEN) (Kreymann *et al.*, 2006:218-220; Singer *et al.*, 2009:394)	2009	Immune-modulating formula enriched with arginine, nucleotides and n-3 FA is indicated in elective upper gastrointestinal (GI) surgical patients (Grade A), patients with mild sepsis (Grade B) or ARDS (Grade B). No recommendations could be made in burns and patients with SAP. Severely ill ICU patients should not receive products enriched with arginine, nucleotides and n-3 FA (Grade B).	EPA- and DHA-containing lipid emulsions influence inflammatory processes and possibly decrease length of stay in ICU (Grade B).

Canadian Critical Care Practice Guidelines (Dhaliwal *et al.*, 2014:43)	2013	Enteral formulations containing n-3 FA and/or borage oil and antioxidants should be considered.	Intravenous lipid emulsions that decrease the amount of n-6 FA/soybean oil content should be considered as there are insufficient data to make concrete recommendations.
American Society of Enteral and Parenteral Nutrition (ASPEN) and Society of Critical Care Medicine (SCCM) (McClave *et al.*, 2016:174,180)	2016	No recommendations can be made regarding the use of enteral formulations containing n-3 FA and/or borage oil in enteral products in patients with ARDS due to lack of evidence.	No recommendation due to a lack of availability of SMOF lipid emulsion but may change when it becomes available.
South African DOH guidelines	2016	None	It is possible that PN lipid emulsions reduce length of stay.

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; ASPEN: American Society of Enteral and Parenteral Nutrition; DOH: Department of Health; EN: Enteral Nutrition; ESPEN: The European Society of Nutrition and Metabolism; FA: Fatty acids; GI: Gastrointestinal; ICU: Intensive Care Unit; PN: Parenteral Nutrition; SAP: Severe acute pancreatitis; SCCM: Society of Critical Care Medicine

2.5.3.5 **Possible application in mechanically ventilated, critically ill patients**

As MV is a common intervention employed in the ICU setting and has a strong underlying inflammatory component, any intervention aiding in the reduction of inflammatory processes could be highly beneficial (Fan *et al.*, 2013:86). A higher amount of lipids alone may influence the time taken to wean from MV; however, the type of lipid is of great importance. It has been demonstrated that intravenous infusion of LCPUFAs was accompanied by a reduction in prostaglandin production and had a favourable effect on ventilatory dynamics, especially related to ventilation/perfusion mismatch by improvement of oxygenation (Singer *et al.*, 2006:1036). This has been demonstrated in patients diagnosed with ALI (Singer *et al.*, 2006:1036). The available studies have found different results regarding the use of n-3 FA in patients on MV and therefore a systematic review is necessary in order to determine if its use is beneficial.

2.6 Conclusion

Critical illness and the invasive procedure of MV remains a necessary but resource-intensive practice, with facilities in SA being limited (Hurri, 2016:1). Nutritional support (NS) has been proved to be a necessary intervention in the ICU setting and this has extended beyond simply meeting basic nutritional requirements (McClave *et al.*, 2016:161; Weijs & Wischmeyer, 2013:194). A lot of research has been done on the use of immunonutrients, which include n-3 FAs (Aqeel *et al.*, 2017:114). As n-3 FAs might play a role in the modulation of the immune response, it is of special interest in this population of critically ill patients receiving MV, considering the underlying inflammatory responses in this situation (Calder, 2013:651). Its addition to artificial nutrition products might have positive effects on the clinical outcomes of critically ill patients (Calder, 2010:565). Recently, studies have been done of different populations of critically ill patients, which include patient groups with sepsis and septic shock, ALI, ARDS, SIRS and trauma (Donoghue *et al.*, 2017:46-47; Manzanares *et al.*, 2015:170). The results of these studies are conflicting and no concrete recommendations can be made. There are various reasons why studies have been shown to be inconsistent in their results. The inflammatory response is a complex interaction of various systems and pathways and might differ depending on disease severity and type of disease or injury, as well as demographic factors.

A thorough review of the available literature has led to the conclusion that there is a lack of studies which included only critically ill patients that were mechanically ventilated. Moreover, these studies seem to be of low quality and there are some differences in the types of outcome measures, which make comparison difficult. The inconsistency in dosages used in the available trials also makes it difficult to determine whether there is a significant clinical benefit with regard to the use of n-3 FAs in critically ill patients on MV. However, the positive results found in some of the trials cannot be disregarded and therefore, based on the possible clinical benefit, further investigation is justified; thus, a systematic review is necessary to provide evidence-based guidelines.

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CHAPTER 3 JOURNAL ARTICLE

Effect of omega-3 fatty acids on clinical outcomes of mechanically ventilated, critically ill patients: a systematic review

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Abbreviations

AA	Arachidonic acid
ALA	α-linolenic acid
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
BAL	Broncho-alveolar lavage
BMI	Body mass index
CI	Critical illness
COPD	Chronic obstructive pulmonary disease
DHA	Docosahexanoic acid
EN	Enteral nutrition
EPA	Eicosapentaenoic acid
GLA	γ-linolenic acid
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICU	Intensive Care Unit
IL	Interleukin
ITT	Intention-to-treat
LCT	Long chain triglycerides
LOS	Length of stay
LOV	Length of ventilation
LTB_5	Leukotriene B5
MV	Mechanical Ventilation
n-3 FA	Omega-3 Fatty acids
n-6 FA	Omega-6 Fatty acids
NF-κB	Nuclear-factor kappa B
NS	Nutrition support
OR	Odds ratio

49	PF ratio	Ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen
50	PGE_3	Prostaglandins E3
51	PN	Parenteral nutrition
52	PRISMA	Preferred reporting items for systematic reviews and meta-analyses
53	RCT	Randomised controlled trials
54	SIRS	Systemic inflammatory response syndrome

Abstract

Introduction: Although mechanical ventilation (MV) is a life-saving strategy, it is associated with serious complications. Early weaning is required to prevent complications related to prolonged ventilation. Many of the conditions indicating the need for MV, and some complications of prolonged MV, have strong inflammatory components. The anti-inflammatory properties of omega-3 fatty acids (n-3 FA) could, therefore, possibly contribute to a reduction in MV days. This systematic review will aim to evaluate existing published trials regarding the effect of n-3 FAs on length of ventilation (LOV) and other clinical outcomes in critically ill, MV patients.

Methods: Electronic searches were conducted in MedLine, Google Scholar, Scopus, EBSCOhost, ScienceDirect, PubMed and Web of Science. Relevant articles, published from 2000 to 2017, were screened and included. Studies comparing standard care or a placebo to enteral or parenteral feeds containing pure fish oil supplementation or fish oil containing lipid emulsions in critically ill, MV patients were included. In total, 12 trials were included, of which eight used enteral and four parenteral feeds. Primary outcomes were length of ventilation (LOV) and the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (PF ratio). Secondary outcomes included Intensive Care Unit length of stay (ICU LOS) and mortality.

Results: None of the results showed any benefit of supplementation with n-3 FA on LOV, mortality or ICU LOS. Parenterally administered n-3 FA did not affect PF ratio in patients on MV. Enteral supplementation improved PF ratio before day seven, where after no effect was observed. There was significant heterogeneity found between the enteral studies and results should thus be interpreted with care. The overall risk of bias across all of the studies included was high.

Conclusion: Supplementation with either enteral or parenteral n-3 FA does not show any benefit regarding the LOV, PF ratio, ICU LOS or mortality in MV, critically ill patients. More randomised controlled clinical trials are required in order to make definitive recommendations.

Introduction

Mechanical ventilation (MV), indicated in critically ill patients unable to maintain homeostasis, can further aggravate the immune response already activated by physiological stress (Fan *et al.*, 2013:86). Critical illness (CI) and its complications, along with prolonged periods of MV, not only negatively impact patient outcomes, but inevitably contribute to increased healthcare costs (Vincent *et al.*, 2014:380). Globally, mortality in Intensive Care Units (ICUs) has been reported to be as high as 16.2%, and even higher in patients with sepsis (Vincent *et al.*, 2014:380).

Omega-3 fatty acids (n-3 FA), specifically eicosapentanoic acid (EPA) and doxosahexanoic acid (DHA), have been investigated as an alternative lipid emulsion to the conventionally used soybean oil-predominant emulsions which contain long-chain triglycerides (LCT) rich in omega-6 fatty acids (n-6 FA) (Calder, 2010:167; Manzanares *et al.*, 2015). However, potent inflammatory eicosanoids are produced from arachidonic acid (AA), a derivative of n-6 FAs (Martin & Stapleton, 2010:532; Vanek *et al.*, 2012:152). On the other hand, EPA and DHA, *via* numerous mechanisms, also have the ability to modulate the inflammatory response in a more favourable way. This includes the production of the anti-inflammatory lipid mediators (Vanek *et al.*, 2012:152). Additionally, the activation of nuclear factor kappa-b (NF-κB) can be inhibited by EPA and DHA and the production of protectins and resolvins can also be triggered (Calder, 2010:566; Calder, 2013:650; Martin & Stapleton, 2010:533). It is due to these mechanisms that n-3 FAs may favourably alter the inflammatory response that results from critical illness.

In an attempt to determine the potential benefit of n-3 FAs on clinical outcomes in critically ill patients, numerous reviews and meta-analyses have been published that include a broad critically ill patient population (Abbasoglu *et al.*, 2017; Donoghue *et al.*, 2017; Lu *et al.*, 2017; Manzanares *et al.*, 2015; Palmer *et al.*, 2013). Included in these reviews were studies conducted on patients with sepsis, septic shock and acute respiratory distress syndrome

(ARDS), as well as trauma patients and general surgical and medical ICU patients (Donoghue *et al.*, 2017:38; Manzanares *et al.*, 2015:167). The results remain conflicting, making it difficult to make definitive recommendations regarding the use of n-3 FA in this patient population (Dhaliwal *et al.*, 2014:43; McClave *et al.*, 2016:180).

Some clinical trials have shown that n-3 FA may contribute to improved ventilatory dynamics, possibly resulting in earlier weaning from MV support (Grau-Carmona *et al.*, 2011:2329; Parish *et al.*, 2014:557; Singer *et al.*, 2006:1035). As MV is associated with various complications, aiming for early weaning is desirable since this can contribute to improved clinical outcomes with regard to ICU LOS and morbidity (Manzanares *et al.*, 2015:167). The aim of this review is to systematically and critically appraise available data regarding the effect of n-3 PUFA administration compared with standard care on the clinical outcomes of those critically ill patients receiving mechanical ventilation.

Methods

The primary outcomes of the review included length of mechanical ventilation (LOV) reported as MV days, and indicators of oxygenation status (PF ratio). Additional outcomes included length of ICU stay, morbidity and/or mortality.

Search strategy

Electronic searches of MedLine, Scopus, EBSCOhost, PubMed and ScienceDirect were conducted to identify relevant randomised controlled trials (RCT) conducted between 01/01/2000 and 31/12/2017. Searches were restricted to studies in English only. Keywords or medical subject headings that were used included “critically ill” “Intensive Care Units”, “ventilation”, “ventilation, mechanical” “fat emulsions, intravenous”, “fish oils”, “parenteral nutrition, total”, “fatty acids, omega-3”, “eicosapentanoic acid”, “docosahexanoic acid” and “enteral nutrition”. Additionally, references from included studies and available systematic reviews were screened for possible additional RCTs. Study selection was made independently

by two different authors (RG and ML). Any disagreements were resolved by the third author (AN). Studies that fulfilled all of the eligibility criteria were included in the systematic review. This systematic review was conducted according to the PRISMA guidelines and the GRADE approach was used to appraise the overall quality of the included studies. The GRADE ranking for the included studies is summarized in Table 1 and 2. The overall quality was based on various factors such as the within-study risk of bias, the heterogeneity of the data, and bias.

Eligibility criteria

Studies were included if i) they were randomised control trials (RCT) (including quasi-RCT); ii) included only critically ill adult patients ≥18 years of age admitted to an Intensive Care Unit (ICU) and requiring invasive MV; iii) the intervention group received fish oil either as a supplement or as part of a product enriched with fish oil *via* either the enteral or parenteral route; iv) the control group also received nutrition support (NS) *via* the same route as the intervention group, consisting of any form of placebo or feed not supplemented with fish oil.

Selection of studies

After searches of all the specified databases, duplicate results were removed. Thereafter, exclusion based on the title was done. The abstracts of the remaining studies were obtained and screened. Lastly, full-text articles were obtained and assessed for eligibility. This process is depicted in Figure 1.

Data extraction

Data extraction was done independently by two authors (RG and ML) using a pre-piloted electronic data extraction sheet. Any disputes were referred to the third author (AN) and discussed until consensus was reached. Where possible, the following data were extracted: i) length of ventilation (LOV), ii) oxygenation status reported as PF ratio, iii) length of stay in ICU (ICU LOS) iv) 28-day mortality and v) morbidity.

Data synthesis

The primary outcome of this review was LOV. Data were analysed using the random effects model in RevMan 5.3 (Cochrane IMS Oxford, UK). Data were separated according to route of administration. Data from EN studies that reported LOV as ventilator-free days were analysed separately. Thereafter, the overall weighted mean difference with 95% confidence intervals for LOV, PF ratio and ICU LOS was determined. Data for mortality (dichotomous) were pooled to estimate the odds ratio (OR) with a 95% confidence interval. Continuous variables are expressed as the mean difference. Analyses of data were based on an intention-to-treat (ITT) principle.

Risk of bias assessment

The Cochrane Collaboration tool was used for the assessment of risk of bias (Higgins *et al.*, 2011:6). Each individual study was assessed across the seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and other sources of bias (Higgins *et al.*, 2011:6). Any disagreements between the two data extractors (RG and ML) were resolved through discussion until consensus was reached.

Assessment of heterogeneity

Where possible, heterogeneity was assessed by visual inspection (RG and ML) of the forest plots and by the Chi^2 test for heterogeneity (a significance level of $P<0.1$ was used). Heterogeneity was further quantified with the I^2 test (Higgins & Thompson, 2002:1539) and I^2 values of > 50% indicated substantial heterogeneity (Higgins & Thompson, 2002:1539; Higgins & Green, 2011:253).

Results

A total of 12 studies were included in this systematic review (Figure 1). Of these studies, four administered an n-3 FA-containing product or supplement parenterally (Barbosa *et al.*, 2010:1;

Friesecke *et al.*, 2008:1411; Grau-Carmona *et al.*, 2015:31; Gupta *et al.*, 2011:108). The remaining eight studies administered the intervention product enterally (Grau-Carmona *et al.*, 2011:578; Kagan *et al.*, 2015:460; Pacht *et al.*, 2003:491; Parish *et al.*, 2014:555; Pontes-Arruda *et al.*, 2006:2325; Rice *et al.*, 2011:1574; Singer *et al.*, 2006:1033; Stapleton *et al.*, 2011:1655). The main reason for the exclusion of trials was that not all patients received MV or that the outcomes reported did not meet the eligibility criteria. The four PN RCTs had an aggregate total of 411 patients while the EN RCTs had a total of 1032 patients.

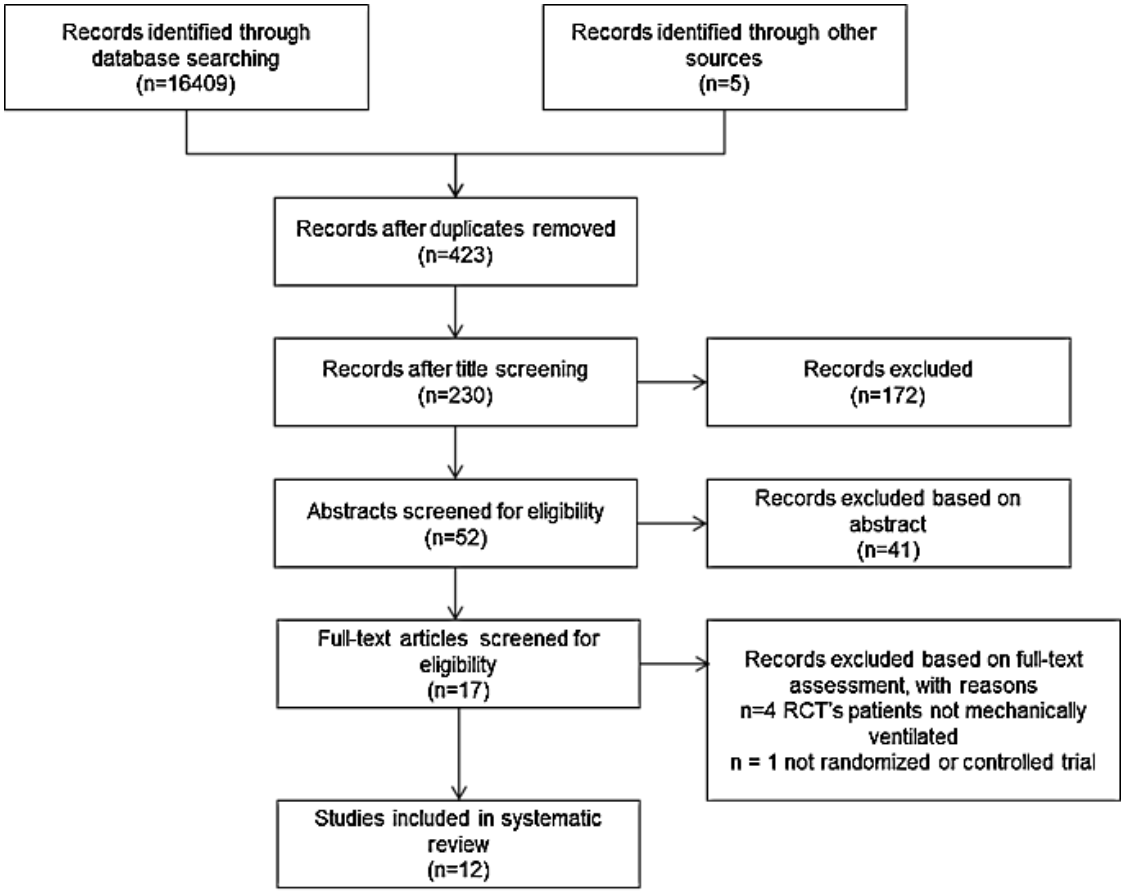

Figure 1 Flow diagram of the literature search

The characteristics of the individual studies included are summarised in Table 3 and Table 4 respectively.

Risk of bias

The level of bias was judged according to the Cochrane Collaboration tool. (Higgins *et al.*, 2011:2). Risk of bias was deemed high if any of the elements assessed was unclear or high

and was considered to be low if all of the assessment areas were low. The risk of bias across both the PN (Figure 2) and EN studies (Figure 3) was found to be high, with the exception of two EN studies conducted by Stapleton *et al.* 2011 and Kagan *et al.* 2015, in which the risk of bias was assessed to be low. This was mostly due to a lack of information, making assessment of risk of bias difficult.

	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Reporting bias)	Other bias
Barbosa 2010	?	+	?	?	?	+	?
Friesecke 2008	+	+	+	+	-	+	?
Grau-Carmona 2015	+	+	+	+	+	+	?
Gupta 2011	+	+	?	?	+	-	?

Figure 4 Risk of bias of PN studies

	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Reporting bias)	Other bias
Grau-Carmona 2011	+	+	-	+	-	+	+
Kagan 2015	+	+	+	+	+	+	+
Pacht 2003	+	?	+	+	?	+	?
Parish 2014	+	-	-	-	+	+	+
Pontes-Arruda 2006	+	?	?	?	-	-	-
Rice 2011	+	+	+	+	+	+	-
Singer 2016	+	-	+	+	?	?	-
Stapleton 2011	+	+	+	+	+	+	+

Figure 5 Risk of bias of EN studies

The quality of the included studies was evaluated using the GRADE ranking. It was found that, for most of the clinical outcomes across the PN and EN studies, quality was very low. The findings of the quality assessment according to GRADE are summarised in Tables 1 and 2.

Table 1: Grading of Recommendations Assessment, Development and Evaluation (GRADE) ranking for PN studies

Outcomes	Number of studies	GRADE ranking	Number of patients followed up	Motivation
LOV at 4 days	2	Very low	84	Blinding and incomplete outcome data were poor for one study. There was inconsistency as significant heterogeneity was seen.
LOV at 7 days	2	Very low	226	Both studies had a high risk of bias. Great inconsistency was seen between the two trials included as assessed by the weighting of the trials. Indirectness was present.
PF ratio	2	Low	84	A high risk of bias was present in both studies. Inconsistency was present as the intervention used was not the same in both trials.
Mortality	4	Very low	454	There was a high risk of bias across all studies. Inconsistencies were detected regarding the intervention and significant heterogeneity was demonstrated.
ICU LOS	3	Low	249	All studies were assessed to have a high risk of bias. Heterogeneity was not significant but there were differences in the interventions used.

Abbreviations: LOV: Length of ventilation; ICU: Intensive care unit; LOS: Length of stay; PF ratio: Ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen

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Table 2: Grading of Recommendations Assessment, Development and Evaluation (GRADE) ranking for EN studies

Outcomes	Number of studies	GRADE ranking	Number of patients followed up	Motivation
LOV at 4 days	2	Very low	280	Both studies had a high risk of bias. Great inconsistency was seen between the two trials included as assessed by the weighting of the trials. Indirectness was observed in the intervention used.
PF ratio at day 7	5	Very low	495	The studies were assessed to have an overall high risk of bias. Inconsistencies were present as the intervention differed between studies and significant heterogeneity was seen.
PF ratio at day 14	3	Very low	301	There was an overall high risk of bias amongst all of the studies included. Heterogeneity was found to be extremely high and the intervention diets differed in each case.
Mortality	4	Low	441	There was a high risk of bias across all studies. Inconsistencies were detected regarding the intervention but no significant heterogeneity was demonstrated.
ICU LOS	4	Low	441	All studies were assessed to have a high risk of bias. Heterogeneity was not significant but there were differences in the interventions used.

Abbreviations: LOV: Length of ventilation; ICU: Intensive care unit; LOS: Length of stay; PF ratio: Ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen.

Length of mechanical ventilation (LOV)

In total, two PN studies reported on LOV (Barbosa *et al.*, 2010:7; Gupta *et al.*, 2011:110). No statistically significant differences were found between the intervention and control groups on study day four or seven (Figure 4 and 5). Heterogeneity between the studies was not significant in either case (I^2=0%) since the Gupta (2011) study contributed the majority of the weight. Results during the first four days indicated a total mean difference of 0.10 [-0.17, 0.38] although the total sample size was very small (n=84), while results at seven days were 0.27 [-0.58, 1.11] with a sample size of 226.

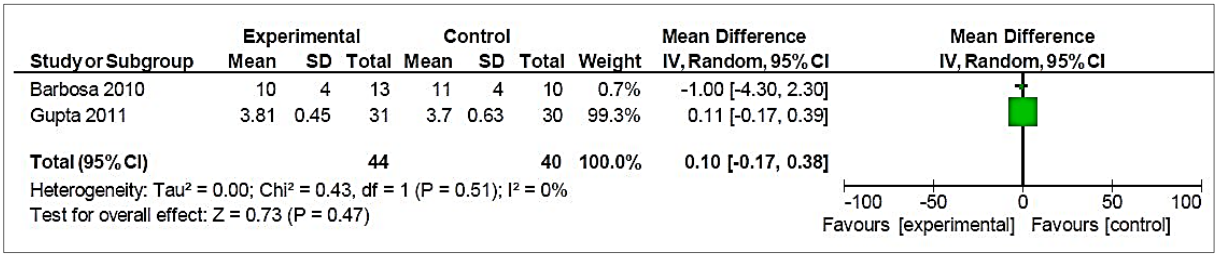

Figure 4 Length of ventilation (LOV) for PN studies at 4 days

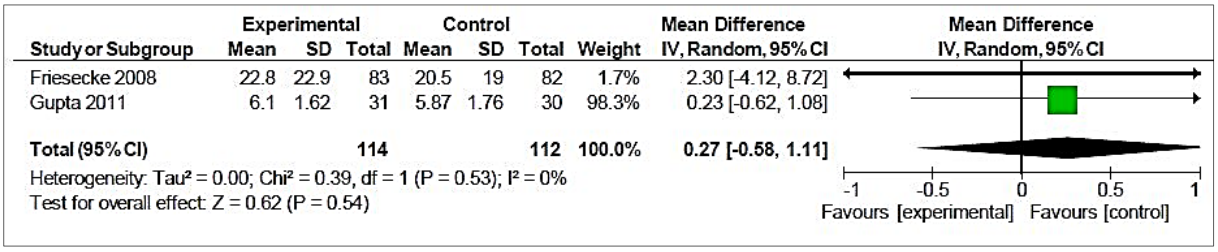

Figure 5 Length of ventilation (LOV) of PN studies at 7 days

Two enteral studies (Grau-Carmona *et al.*, 2011:582; Kagan *et al.*, 2015:462) reported LOV. No significant difference was demonstrated between the experimental and control groups (Figure 6). However, heterogeneity between the two studies was significant (I^2=61%) with a total mean difference of -0.75 [-4.32, 2.82].

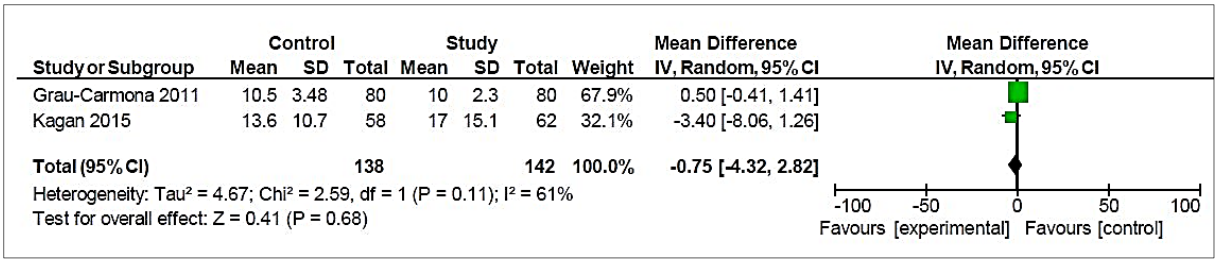

Figure 6 Length of ventilation (LOV) of EN studies reported as MV days

Three enteral studies reported LOV as ventilator-free days (Parish *et al.*, 2014:557; Pontes-Arruda *et al.*, 2006:2329; Rice *et al.*, 2011:1576). Both the studies conducted by Pontes-Arruda *et al.* (2006) and Parish *et al.* (2014) found that the intervention had a significant effect on LOV (Parish *et al.*, 2014:555; Pontes-Arruda *et al.*, 2006:2329). To the contrary, the study conducted by Rice *et al.* (2011) demonstrated that the intervention had the opposite effect on LOV and the study was suspended early (Rice *et al.*, 2011:1579). When pooled, no effect was observed (Figure 7). Heterogeneity between the studies was extremely high (I^2=99%), with a total mean difference of -3.62 [-9.32, 2.08].

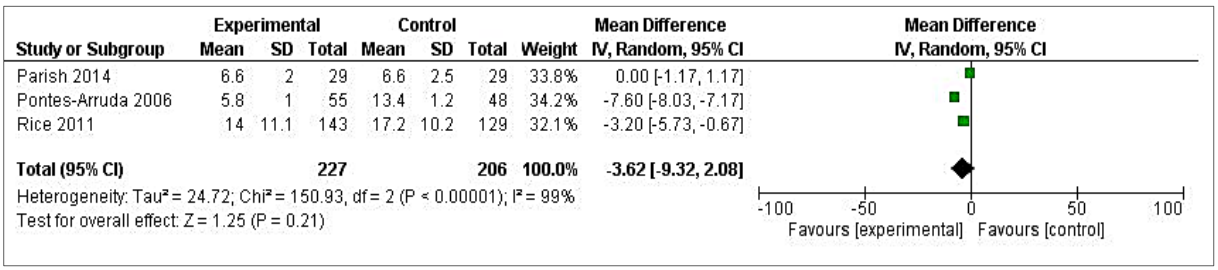

Figure 7 Length of ventilation (LOV) of EN studies reported as ventilator-free days

The results by Singer *et* al. (2006) were not pooled as LOV was reported as ventilator-free hours (Singer *et al.*, 2006:1035). These authors did, however, find a significant decrease in LOV, favouring the intervention that consisted of a EN formula containing n-3 FA and GLA (Singer *et al.*, 2006:1035).

Ratio of arterial oxygen partial pressure to fractional inspired oxygen (PF ratio)

Two PN studies reported PF ratio as one of the outcomes (Barbosa *et al.*, 2010:7; Gupta *et al.*, 2011:111). There was no statistical difference between the experimental and control groups with regard to this specific indicator of oxygenation (Figure 8). Heterogeneity was high (I^2=54%), indicating additional factors influencing the results.

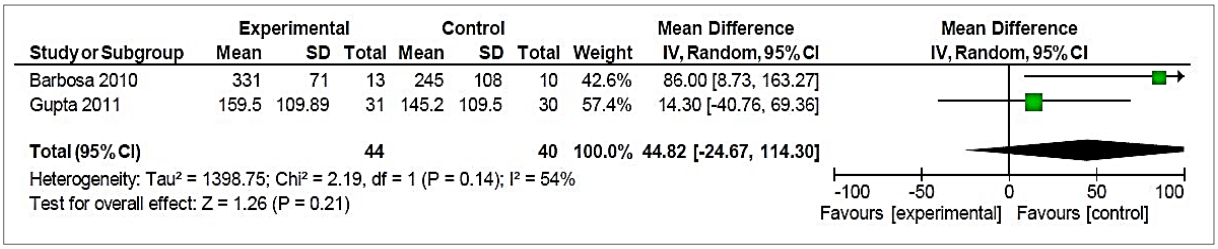

Figure 8 PF ratio of PN studies

Enteral nutrition studies reported PF ratio at different time intervals. Five studies reported LOV on day seven after patient enrolment (Figure 9) (Grau-Carmona *et al.*, 2011:582; Kagan *et al.*, 2015:462; Parish *et al.*, 2014:557; Singer *et al.*, 2006:1035; Stapleton *et al.*, 2011:6). Of these, three studies reported results on day 14 (Figure 10) (Grau-Carmona *et al.*, 2011:582; Parish *et al.*, 2014:557; Singer *et al.*, 2006:1035).

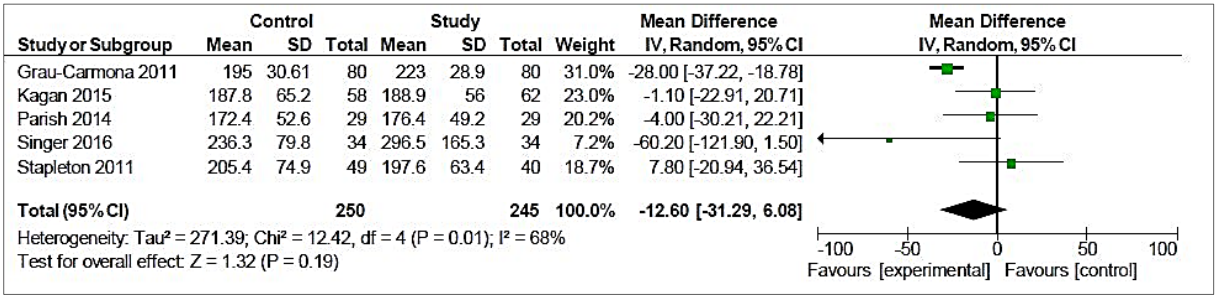

Figure 9 PF ratio of EN studies on day 7

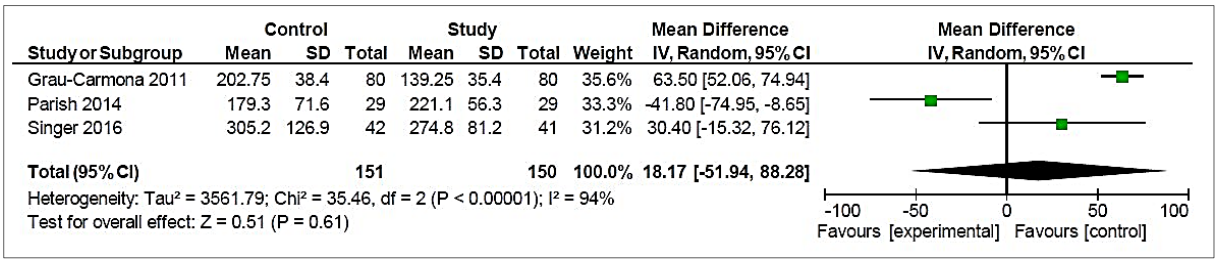

Figure 10 PF ratio of EN studies on day 14

On day seven, there was no significant difference between the control and experimental groups. Heterogeneity was found to be significant (I^2=68%) between the included studies (Figure 9). The analysis of PF ratio on day 14 also did not yield any significant effects (Figure 10). In this case, heterogeneity was found to be very high (I^2=94%) indicating great variation in the populations included.

Mortality

There was no mortality benefit of n-3 FA supplementation in either the PN or EN studies. Four studies using PN were included (Barbosa *et al.*, 2010:8; Friesecke *et al.*, 2008:1417; Grau-Carmona *et al.*, 2015:37; Gupta *et al.*, 2011:112). No significant effect was observed (OR 0.86 [0.41, 1.79] with significant heterogeneity between the included studies (I^2=57%) (Figure 11).

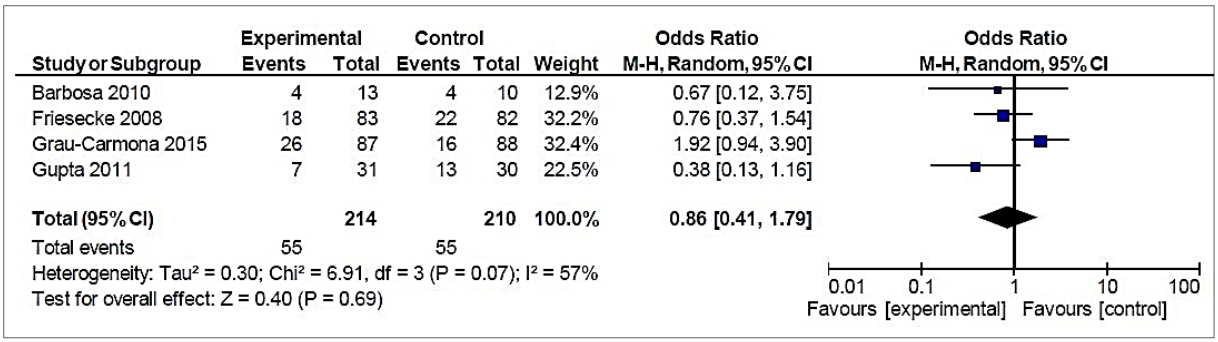

Figure 11 Twenty-eight-day mortality of PN studies

The results of the four EN studies were pooled. Omega-3 FA (n-3 FA) did not have a significant effect on 28-day mortality, as seen in Figure 12 (Grau-Carmona *et al.*, 2011:582; Kagan *et al.*, 2015:466; Parish *et al.*, 2014:557; Pontes-Arruda *et al.*, 2006:2328). Heterogeneity was not significant (I^2=15%). However, three of the included EN studies used a product containing n-3 FA as well as other immune-modulating nutrients whereas Parish *et al.* (2014) was the only study using a pure fish oil supplement. For EN, the 28-day mortality OR was 1.30 [0.77, 2.21].

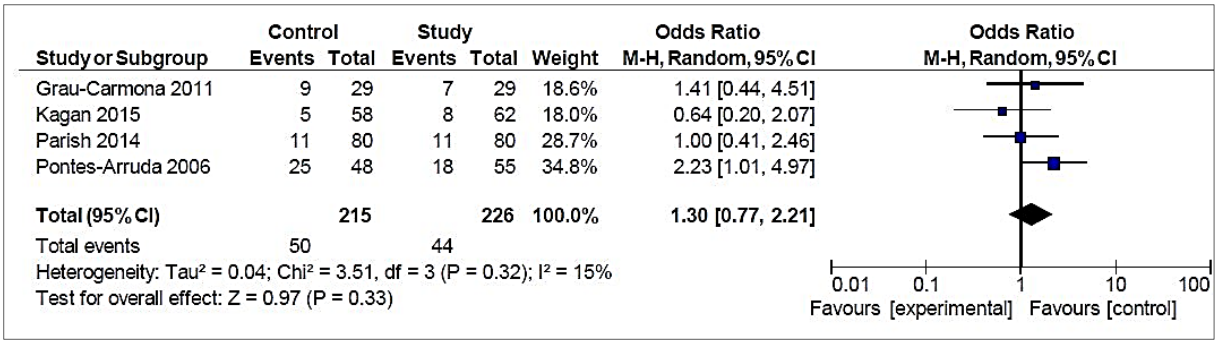

Figure 12 Twenty-eight-day mortality of EN studies

Length of stay in ICU

Length of stay in ICU of the experimental and control groups of the PN studies was also not found to be significantly different (See Figure 13) (Barbosa *et al.*, 2010:8; Friesecke *et al.*, 2008:1417; Gupta *et al.*, 2011:112). Heterogeneity was not significant (I^2=23%). Pontes-Arruda *et al.* (2006) reported their results for this clinical outcome as ICU-free days and therefore their results could not be included in the analysis (Pontes-Arruda *et al.*, 2006:2329). Using a product containing n-3 FA, GLA and antioxidants, the authors reported significantly more ICU-free days in the intervention group (Pontes-Arruda *et al.*, 2006:2329).

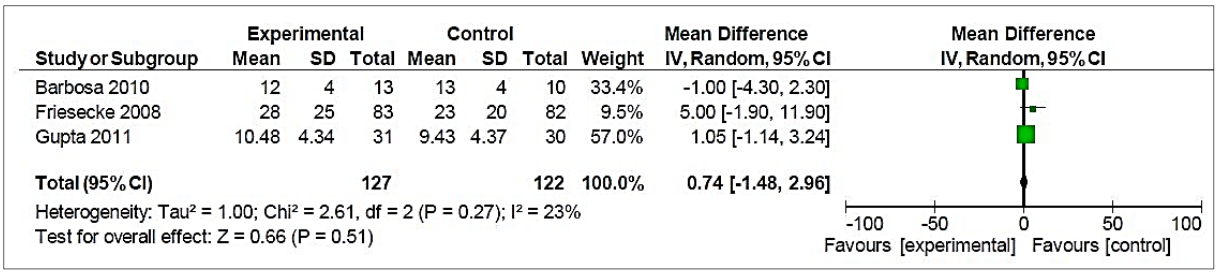

Figure 13 Length of stay in ICU of PN studies

No effect was found regarding ICU LOS when the results of the three included EN studies were pooled (Figure 14) (Barbosa *et al.*, 2010:8; Friesecke *et al.*, 2008:1417; Gupta *et al.*, 2011:112; Kagan *et al.*, 2015:466). The heterogeneity of the studies was low (I^2=15%) with an OR of 2.23 [1.01, 4.97].

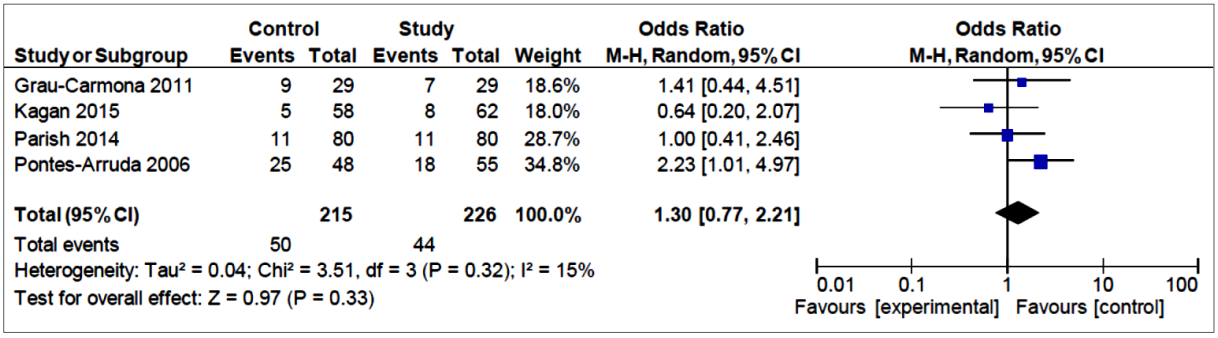

Figure 14 Length of stay in ICU of EN studies

Table 3: Studies of MV patients on PN

Authors	Year	n	Patients	Duration (Days)	Intervention		Findings
					Control diet	Study diet	
Barbosa *et al.*	2010	25	Patients diagnosed with sepsis or SIRS	6	50:50 mixture of MCT:LCT	50:40:10 mixture of MCT:LCT:Fish oil	No difference in PGE_2 or LTB_4 levels, IL-6 levels decreased significantly more in the intervention group No difference between the groups regarding LOV, ICU LOS or mortality
Friesecke *et al.*	2008	166	Medical ICU patients stratified according to presence or absence of SIRS	7	1:1 mixture of MCT:LCT with a n3:n6 ratio of 1:7	1:1 mixture of MCT:LCT supplemented with fish oil resulting in a n3:n6 ratio of 1:2 given as a separate infusion, making up a total of 17% of the total amount of lipid given	No significant differences between the two groups in IL-6 levels, incidence of nosocomial infections, LOV, ICU LOS or 28-day mortality
Gupta *et al.*	2011	61	Medical ICU patients with suspected ARDS	14	Standard isonitrogenous, isocaloric enteral diet	Standard isonitrogenous, isocaloric enteral diet with parenteral omega-3 fatty acids with a ratio of n3:n6 of 1:2	No difference in PF ratio, LOV or LOS ICU or hospital LOS
Grau-Carmona *et al.*	2015	159	Medical and surgical ICU patients	>5	A lipid emulsion containing 50% MCT and 50% LCT	A lipid emulsion containing 50% MCT, 40% soybean oil (LCT) and 10% fish oil	Significant decrease in the risk of developing nosocomial infections in the intervention group No statistically significant decrease in LOV, ICU LOS or hospital LOS

Abbreviations: MCT: Medium-chain triglycerides; LCT: Long-chain triglyceride; PGE_2: Prostaglandin E_2; LTB_4: Leukotriene B_4; IL-6: Interleukin-6; LOV: Length of ventilation; ICU: Intensive care unit; SIRS: Systemic inflammatory response syndrome; LOS: Length of stay; ARDS: Acute respiratory distress syndrome; PF ratio: Ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen

Table 4: Studies of MV patients on EN

Authors	Year	n	Patients	Duration (Days)	Intervention		Findings
					Control diet	Study diet	
Pacht *et al.*	2003	67	Patients with ALI or ARDS	7	Ready-to-feed high fat, low carbohydrate enteral nutrition formula designed to reduce CO_2 production	EPA and GLA containing enteral formula	Significantly reduced pulmonary inflammation, increased oxygenation and improved clinical outcomes were seen in patients receiving the study diet
Pontes-Arruda *et al.*	2006	165	ICU patients with severe sepsis or septic shock	28	High-fat, low carbohydrate enteral formula that was balanced for patients with pulmonary disease with a ratio of n3:n6 of 1:3.8	Product enriched with EPA, GLA and antioxidants with a ratio of n3:n6 of 1:1.85 providing 4.5g EPA, 2.0g DHA and 4.3g GLA per litre of product	Significant difference in ventilator-free days and ICU-free days in group receiving study diet Significant difference in PF ratio favouring the study diet group
Singer *et al.*	2006	100	Ventilated patients with ALI	14	Ready-to-feed, high-fat, low-carbohydrate enteral formula	Enteral feed that differed only in lipid composition as it contained supplemental GLA and EPA, as well as higher levels of antioxidants	Oxygenation was significantly higher in the study group; however, the effect was lost by day 14 Study group had significantly shorter LOV No difference in LOS
Stapleton *et al.*	2011	90	Patients diagnosed with ALI	14	0.9% Saline placebo administered enterally	Concentrated liquid fish oil administered enterally: 7.5 cc every 6 hours equalling 9.75g EPA and 6.75g DHA daily	No difference in BAL IL-8, IL-6 or LTB_4 No significant difference in LOV, ICU LOS or hospital LOS
Grau-Carmona *et al.*	2011	160	Patients with ALI/ARDS and sepsis	28	The control diet had a ratio of 90:1 non-protein calories to nitrogen and the ratio of n3:n6 was 1:5.8	The study diet had a non-protein calorie to nitrogen ratio of 94:1 and a ratio of n3:n6 was 1.5:1	No difference in PF ratio of LOV Similar incidence of infections

Rice *et al.*	2011	272	Patients with ALI	28	The control supplement (Isocaloric-isovolemic) was administered enterally as twice-daily boluses of 120ml beginning within 6 hours of randomisation and was identical in appearance and smell to the deodorised n-3 supplement	The n-3 supplement was administered enterally as twice-daily boluses of 120ml beginning within 6 hours of randomisation	The study was stopped early due to futility. Patients in the intervention group had fewer ventilator-free days, fewer ICU-free days and fewer days free of non-pulmonary organ failure
Parish *et al.*	2014	58	Patients with mild to moderate ARDS	14	25kcal/kg isocaloric, isovolemic, carbohydrate-rich enteral formula *via* nasogastric tube or PEG feeding tube	Six n-3 soft gel capsules per day (2 capsules every 8 hours) in addition to the standard treatment. Each soft gel capsule contains 360mg EPA and 240mg DHA	Supplementation with n-3 FA had positive effects on LOV and oxygenation
Kagan *et al.*	2015	120	Patients with severe trauma	7	High-fat, low-carbohydrate enteral formula	Enteral formula enriched with EPA, GLA and antioxidants	No significant difference between the control and study groups was found for PF ratio, LOV, ICU LOS or 28-day mortality

Abbreviations: ARDS: Acute respiratory distress syndrome; ALI: Acute lung injury; BAL: Broncho-alveolar lavage; EPA: Eicosapentanoic acid; DHA: Doxosahexaenoic acid; GLA: gamma-linolenic acid; LTB_4: Leukotriene B_4; IL-8: Interleukin-8; IL-6: Interleukin-6; LOV: Length of ventilation; ICU: Intensive care unit; LOS: Length of stay; PF ratio: Ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen

Discussion

Previous research has demonstrated that the supplementation of n-3 FA may be a promising approach to improve various clinical outcomes in critically ill patients (Grau-Carmona *et al.*, 2015:36; Pacht *et al.*, 2003:496; Parish *et al.*, 2014:557; Pontes-Arruda *et al.*, 2006:2329; Singer *et al.*, 2006:1035). Although the importance of general NS in the critical care setting has been well established, recommendations with regard to the use of n-3 FA to decrease LOV and ICU LOS, specifically, remain inconclusive (Dhaliwal *et al.*, 2014:43; McClave *et al.*, 2016:180). Moreover, when investigating its possible benefit in the subset of critically ill patients that require MV, even less data is available to enable recommendations to be made for either PN or EN supplementation. Considering the fact that MV is an extremely invasive procedure that poses a serious risk of numerous complications, any methods of reducing LOV should be explored (Beitler *et al.*, 2016:633; Burns *et al.*, 2013:1). Therefore, investigating n-3 FA supplementation as a possible strategy to aid in early weaning from MV can be of great benefit. The results of this review are discussed separately according to route of administration for ease of interpretation of the results.

The effects of parenterally administered omega-3

Studies conducted with parenterally administered n-3 FA in critically ill, MV patients are very limited and the available studies are of poor quality with an overall high risk of bias. Two studies investigated the effect on n-3 FA on LOV (reported as MV days) on day 4 after initiation of the respective studies and both reported that no reduction in LOV was observed (Barbosa *et al.*, 2010:9; Gupta *et al.*, 2011:112). The same was indicated by the statistical analysis of available data on day 7. Of note is that the weighting of the study conducted by Gupta *et al.* (2011) contributed more than 98% in the statistical analysis of LOV at both day four and day seven. As expected, the results of this analysis merely reflect those found by the abovementioned authors (Gupta *et al.*, 2011:112). The risk of bias in the study by Gupta *et al.* (2011) was found to be high, thus making meaningful conclusions regarding PN n-3 FA and LOV extremely difficult. When all

the available data were combined, irrespective of the number of days on MV, the weighting was more equally distributed but still no beneficial effect of n-3 FA supplementation was observed.

The most recent study included in this review was conducted by Grau-Carmona *et al.* (2015) which, when assessed, had the lowest risk of bias. Although the authors found a reduced risk of nosocomial infections with the use of an n-3 FA-enriched PN product; they failed to show any benefit in terms of LOV (Grau-Carmona *et al.*, 2015:37). The included studies that preceded the study conducted by Grau-Carmona *et al.* (2015) also failed to prove that parenteral n-3 FA decreased LOV (Barbosa *et al.*, 2010:R5; Friesecke *et al.*, 2008:1417; Gupta *et al.*, 2011:112). Both the studies by Gupta *et al.* (2011) and Friesecke *et al.* (2008) failed to prove any beneficial effect of n-3 FA supplementation on any of the clinical outcomes that they evaluated (Friesecke *et al.*, 2008:1411; Gupta *et al.*, 2011:108). The characteristics of the studies, including sample sizes and risk of bias, varied widely, as did the diagnosis of the patients, all of which are factors that may influence the results.

A recent review and meta-analysis showed that infection rate may be decreased and also indicated a trend towards decreased LOV in patients receiving PN fish oil emulsions *vs* predominantly soybean oil-based products. This patient populations of the studies included in the review by Manzanares *et al.* (2015) also included a very heterogeneous patient population; however, the results were not interpreted at separate time intervals and the inclusion criteria differed in that, in our review, only studies in which all patients were ventilated, were included. (Manzanares *et al.*, 2015:170). However, this did not reach statistical significance and no tendency towards decreased mortality was observed, supporting the findings of this review (Manzanares *et al.*, 2015:174). A narrative review by Abbasoglu *et al.* (2017) also came to the conclusion that, from available RCTs, there is little evidence that n-3 FA-containing PN has any effect on the clinical outcomes in a broad population of adult patients (Abbasoglu *et al.*, 2017:1). The findings of this review, which included an aggregate sample size of 411 patients from four studies, was in keeping with the individual results of the included studies, as well as those reported

by preceding reviews and meta-analyses. Although the results all indicate no beneficial effect of n-3 FA supplementation on clinical outcomes, the lack of high-quality evidence and unwanted high heterogeneity in the study populations used still makes it difficult to draw any definitive conclusions.

The effects of enterally administered omega-3

After analysis of the available trials, no beneficial effect was demonstrated with regard to the use of EN n-3 FA in critically ill patients on MV on any of the specified clinical outcomes. This is comparable with a meta-analysis published by Manzanares *et al.* (2015), in which they demonstrated only a tendency towards LOV and mortality in a subgroup of patients that received MV (Manzanares *et al.*, 2015:174).

The results of this review indicated that there was no effect of EN n-3 FA supplementation on LOV. Two of the trials included in the analysis found that the use of n-3 FA did, in fact, significantly reduce the LOV in critically ill patients (Parish *et al.*, 2014:556; Pontes-Arruda *et al.*, 2006:2325). It is important to note that, although all patients were mechanically ventilated, the diagnosis of the patients included in the trials was different and, when taking into consideration the pathophysiology of the different conditions, there is an inherently implied difference in the level of inflammation. It has been demonstrated that the effect of n-3 FA is dose-dependent (Abbasoglu *et al.*, 2017:11). It can therefore be reasoned that, as the effect of n-3 FA is attributed to its role in the inflammatory response, varying degrees of inflammation will have to be taken into consideration and the dose of n-3 FA adapted accordingly in order to achieve the desired effect. Additionally, the possibility exists that separate clinical outcomes are affected by different doses (Abbasoglu *et al.* 2017:9). For example, a positive effect on mortality has been demonstrated with doses of between 0.1 and 0.2 g/kg/day of fish oil, whereas the duration of both ICU and hospital stay has been shown to decrease with doses above 0.05 g/kg/day (Abbasoglu *et al.* 2017:11) This could be a possible cause of the mixed results found in the included trials. Also, those patients diagnosed with severe sepsis or septic shock, as well as patient populations with severe

ARDS, have an overall poorer prognosis than patients diagnosed with ALI. All of the abovementioned factors could explain the high levels of heterogeneity found with the analysis of LOV. In addition, both the study and control diets differed in each trial, further contributing to heterogeneity.

Six out of the total of eight studies investigating the administration of n-3 FA *via* the enteral route used products containing not only EPA and DHA, but also gamma-linolenic acid (GLA) and high levels of antioxidant micronutrients (Table 4). The role of n-3 FA in the modulation of inflammation has been well established (Calder, 2010:567). However, it is possible that the addition of GLA might also affect inflammatory processes by shifting the pathway to favour the production of less pro-inflammatory lipid mediators (Martin & Stapleton, 2010:533). Therefore, in the presence of other additives such as GLA, the effect shown cannot be attributed solely to n-3 FA. The only RCT included in this systematic review that used a pure fish oil supplement and not the combination of EPA, DHA, GLA and antioxidants was conducted by Stapleton *et al.* (2011), and no beneficial effect on any of the outcomes related to MV was demonstrated (Stapleton *et al.*, 2011:1655). Pontes-Arruda *et al.* (2006) demonstrated that n-3 FA, in combination with GLA and antioxidants, did improve the clinical outcomes of critically ill patients with sepsis or septic shock (Pontes-Arruda *et al.*, 2006:2325). Other trials that used the same study diet, have failed to repeat these results. The studies did, however, differ greatly with regard to the diagnosis of the patients included, as was the case with all of the included studies.

As was the case with LOV, this review also failed to indicate that there is any beneficial effect of enteral n-3 FA on PF ratio, 28-day mortality or ICU LOS. The issue of heterogeneity again proved to be problematic and is also attributable to the great variation in patient populations, studies and interventions used. Even though this review included only studies in which all patients were ventilated, the underlying illness and indication for ventilation introduces a host of factors that can affect the inflammatory response, making evaluation of any effect of n-3 FA challenging.

Overall, the supplementation of n-3 FA was considered to be safe and adverse events that occurred did not differ between the control and intervention groups (Abbasoglu *et al.*, 2017:11; Friesecke *et al.*, 2008:1418; Grau-Carmona *et al.*, 2015:31; Gupta *et al.*, 2011:112). This review did have some limitations, specifically regarding the assessment of the quality of the included trials. Generally, there was insufficient information available to allow for adequate assessment of methodology used and the appropriateness of the statistical analyses performed. The delimitation of the language of the studies included could also be considered to be a limitation.

Conclusion

Although the use of n-3 FA was considered to be safe and there was no difference between the control and the intervention groups in the adverse events that occurred, this review did not demonstrate that there is sufficient evidence to recommend the use of n-3 FA *via* either PN or EN administration on the specified clinical outcomes in critically ill, ventilated patients.

This review did, however, highlight the need for more randomised controlled clinical trials in ventilated, critically ill patients to determine whether supplementation with n-3 FA truly has an effect on clinical outcomes, especially LOV. These trials should be designed in such a manner that the only variable is the content of n-3 FA and its ratio to n-6 FA should be appropriate which, according to current evidence, seems to be between 1:2 and 1:4 (Donoghue *et al.*, 2017:41). Separate studies need to be done in different populations of critically ill patients according to illness severity and the level of inflammation. The different stages of critical illness should also be taken into consideration. As inflammation has a direct effect on the outcomes of critically ill patients, this topic is relevant and further investigation is warranted.

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CHAPTER 4 OVERALL DISCUSSION AND CONCLUSION

4.1 Introduction

The investigation of nutrients as pharmacological agents is not a new concept; however, concrete recommendations for the use of n-3 FA in ICU remain unavailable as studies published still demonstrate conflicting results (Abbasoglu *et al.*, 2017:1; McClave *et al.*, 2016:174). The rationale for the addition of n-3 FA from fish oil in nutritional products used in the critically ill population stems from the immunological properties EPA and DHA specifically (Calder, 2015a:26S; Calder, 2015b:469).

Although n-3 FA have been extensively investigated in various chronic health conditions, their precise use and possible benefit in the critical care setting remain uncertain, mainly due to the lack of high-quality clinical trials (Donoghue *et al.*, 2017:45). When this population is further limited to those critically ill patients on MV, the data available become very sparse. Therefore, this systematic review was done in order to extract all available data on this topic.

For ease of reference, the two objectives of this review are listed below:

- To investigate the effect of parenterally administered n-3 FAs on the clinical outcomes of mechanically ventilated, critically ill patients when compared with standard care.
- To investigate the effects of enterally administered n-3 FAs on the clinical outcomes of mechanically ventilated, critically ill patients when compared with standard care.

Four specific clinical outcomes were considered namely length of MV, PF ratio, ICU LOS and mortality. The same clinical outcomes were investigated for both feeding routes, as stated above. Studies were screened systematically by two of the authors after searches were conducted in EBSCOhost, MedLine, Google Scholar, Scopus, ScienceDirect, PubMed and Web of Science, using relevant search terms. An eligibility form was developed to identify the studies that could be included (Addendum A). Data were extracted and summarised per study. A risk of bias assessment was also done for each study. The summary of findings and risk of bias tables for the PN studies are presented in Addendum B and those for the EN studies in Addendum C. PRISMA guidelines were followed throughout this process and the PRISMA checklist is included in Addendum D (Moher *et al.*, 2009:4).

4.2 Omega-3 fatty acids in parenteral nutrition

There are various commercial parenteral fat emulsions available in which the n-6: n-3 ratio ranges between 9:1 and 1:8, the latter of which is an emulsion with a high fish oil content (Donoghue *et al.*, 2017:46). The first-generation lipid emulsions consisted of soybean oil, which has a high amount of n-6 FA, and these FA have been shown to be more pro-inflammatory (Calder, 2010:566; Donoghue *et al.*, 2017:40). Methods of dilution, which include the addition of medium-chain triglycerides (MCT), have been introduced in order to decrease the n-6 FA content, (Calder, 2010:566). Studies focusing on the effect of the addition of fish oil to parenteral nutrition products found positive results in terms of the incidence of new organ dysfunction, infection rate and length of stay although these results from the available RCTs are not consistent (Donoghue *et al.*, 2017:47).

In order to address the first objective, data was extracted from studies conducted in critically ill patients on MV that received predominantly PN n-3 FA. Following the initial search and selecting the studies that met the set inclusion criteria, only four studies were analysed. The summary of findings from each of these studies is presented in Addendum B. No significant differences were found between the study and control groups with regard to any of the stipulated clinical outcomes.

4.3 Omega-3 fatty acids in enteral nutrition

The second objective was to determine the effect of enterally administered n-3 FA on the specified clinical outcomes. Among the eight included studies, different products and patient populations were studied. The details of each study are summarised in Addendum C. A commercially available enteral product that contains EPA, DHA, GLA and antioxidants was the study diet of five of the RCTs included in this review (Grau-Carmona *et al.*, 2011:580; Kagan *et al.*, 2015:462; Pacht *et al.*, 2003:491; Pontes-Arruda *et al.*, 2006:2327; Singer *et al.*, 2006:1034). Pontes-Arruda *et al.* (2006) and Singer *et al.* (2006) found positive effects on LOV and PF ratio with the use of this combination of fatty acids and antioxidants in patients with sepsis and ALI respectively (Pontes-Arruda *et al.*, 2006:2329; Singer *et al.*, 2006:1035). Similarly, Pacht *et al.* (2003) demonstrated positive effects on pulmonary inflammation and oxygenation (Pacht *et al.*, 2003:495). Subsequent RCTs by Grau-Carmona *et al.* (2011) and Kagan *et al.* (2015) failed to reproduce these positive results using the same product (Grau-Carmona *et al.*, 2011:581; Kagan *et al.*, 2015:465).

Stapleton *et al.* (2006) conducted a study in which they examined the effects of a concentrated liquid fish oil emulsion vs a saline placebo (Stapleton *et al.*, 2011:1657). They found no significant difference between the study and control groups with regard to inflammatory markers, length of

MV, ICU length of stay or mortality (Stapleton *et al.*, 2011:1656). The authors concluded that n-3 supplementation is ineffective in improving clinical outcomes in critically ill patients (Stapleton *et al.*, 2011:1661). This particular RCT had a low risk of bias and is the only available trial that used pure fish oil as bolus supplementation. This specific study highlights the need for more studies investigating the independent effect of n-3 FA in order to confirm the results found by Stapleton *et al.* (2006). Parish *et al.* (2014) was the only other RCT included in this systematic review that used a pure fish oil supplement that was in the form of soft-gel capsules (Parish *et al.*, 2014:556). They also failed to show any benefit of n-3 FA supplementation on LOV, ICU LOS and mortality although some benefit on indicators of oxygenation was demonstrated (Parish *et al.*, 2014:557).

4.4 Factors influencing the quality of available trials

There are numerous factors that affect not only the quality of RCTs but also the comparability of these RCTs in a systematic review or meta-analysis with the aim of making recommendations to be implemented in clinical practice.

4.4.1 Weaning protocols and defining clinical outcomes

It is recommended that all ICUs have a protocol in place to aid in decision making with regard to the process of weaning from MV as it has been shown that the use of weaning protocols can affect LOV (BouAkl *et al.*, 2012:44; Zein *et al.*, 2016:67). Subjective aspects in weaning protocols can influence any outcomes related to MV, thus complicating interpretation of results. Preferably, a standardised protocol should be used for the sake of consistency across trials. One example would be the ARDS network protocol that was used in some of the studies included (Grau-Carmona *et al.*, 2011:580; Parish *et al.*, 2014:556; Stapleton *et al.*, 2011:1657). The remaining studies left decisions involving ventilation and weaning to the discretion of the attending physician, thus increasing subjectivity.

One of the key problems in comparing results from RCTs performed in MV patients is the inconsistency of the definition of clinical outcomes (Blackwood *et al.*, 2014:886). This negatively influences evaluation of treatment effects and influences the conclusions of systematic reviews as dilution of the true influence of an intervention is possible (Blackwood *et al.*, 2014:886). It is necessary, therefore, to standardise these definitions in order to improve the accuracy of results (Blackwood *et al.*, 2014:886). Morbidity is one of the clinical outcomes in which this could be problematic. The definition of nosocomial infections in the trial by Grau-Carmona *et al.* (2011) and Pontes-Arruda *et al.* (2006) was in accordance with that of the Centres for Disease Control and Prevention (CDC) guidelines, which is ideal as it is globally accepted and minimises the risk of dilution of effects seen.

4.4.2 Risk of bias

The Cochrane Collaboration tool was used to determine risk of bias in all studies included (refer to Addendum B) (Higgins *et al.*, 2011:348). Studies were assessed with regard to random sequence generation, allocation concealment, blinding, outcome assessment, incomplete outcome data, selective reporting and other sources of bias. The overall risk of bias in terms of random sequence generation was low as the method of randomisation was well described in all the studies (Addendum B). Performance bias was found to be one of the more prevalent types of bias (Barbosa *et al.*, 2010:2; Grau-Carmona *et al.*, 2011:579; Gupta *et al.*, 2011:109; Parish *et al.*, 2014:555; Pontes-Arruda *et al.*, 2006:2326). Additionally, attrition bias was widespread amongst the trials included (Barbosa *et al.*, 2010:5-7; Friesecke *et al.*, 2008:1416; Grau-Carmona *et al.*, 2011:582; Pacht *et al.*, 2003:494; Singer *et al.*, 2006:1035). Additional sources of bias were difficult to assess as reporting on various aspects within the trials was poor (Addendum B). Future studies should aim to address all sources of bias appropriately.

4.4.3 Confounding factors

Studies are subject to confounders that can negatively influence measurement of treatment. Confounding factors relating specifically to the studies included in the systematic review will be discussed in the sections below.

4.4.3.1 **Factors relating to nutritional management**

From a thorough review of the available trials it has become apparent that one of the main confounding factors is control of dietary intake. The composition of the study and the control diets was generally well reported; however, only some studies properly recorded and reported on actual dietary intake (Friesecke *et al.*, 2008:1415; Grau-Carmona *et al.*, 2015:34; Grau-Carmona *et al.*, 2011:582; Kagan *et al.*, 2015:463; Pacht *et al.*, 2003:495; Rice *et al.*, 2011:1577; Stapleton *et al.*, 2011:1660). Both the total amount of fat as well as total energy provided could influence ventilatory dynamics (Doley *et al.*, 2011:235). The trial by Barbosa *et al.* (2010) reported significantly higher carbohydrate intake in the group receiving the intervention and reported no effect of n-3 FA on LOV, a result that could possibly be contributed by this difference (Barbosa *et al.*, 2010:4,7; Doley *et al.*, 2011:235).

There was great variability in both the study and control diets of the trials included (Addendum B). In the EN studies that used a product containing n-3 FA with antioxidants and GLA, a control product was used that had the same amount of fat but differed in its fatty acid composition (Grau-Carmona *et al.*, 2011:580; Pacht *et al.*, 2003:493; Pontes-Arruda *et al.*, 2006:2327; Singer *et al.*,

2006:1034). However, the independent effect of n-3 FA cannot be established in these trials as the control diet contained much lower amounts of antioxidants, which could have a significant impact on outcomes. Ideally, both the study and the control diet should contain the same quantity of antioxidants in order to determine the independent effect of n-3 FA.

In an attempt to have more comparable studies, the feed or supplement should also be administered in the same way. Instead of administering the study product continuously, as was done in the other studies, Rice *et al.* (2011) administered a pure fish oil supplement as a bolus (Rice *et al.*, 2011:1576). It is not clear how this can influence ventilatory or other clinical outcomes; however, Singer *et al.* (2006) reported on observations from a previous study that showed a positive effect on oxygenation related to the increased prostaglandin production following rapid bolus infusions of LCFA (Singer *et al.*, 2006:1036).

4.4.3.2 **Factors relating to medical management**

It has been shown that illness severity scoring correlates directly with clinical outcomes, specifically, mortality and LOS (Breslow & Badawi, 2012:245). Therefore, illness severity scoring could play a role and should be controlled for statistically. Not all studies controlled for illness severity scoring in the baseline analysis, or else they did not report on this aspect.

The infusion of propofol in ICU patients could also potentially influence results. As propofol is not water soluble it is prepared in a soybean emulsion which is high in n-6 FA (Hastings *et al.*, 2017:1). A recent study evaluated the contribution of propofol to total energy intake and found that it significantly increased total energy intake, especially during the first few days after ICU admission as energy requirements seem to be lower in this phase of critical illness (Hastings *et al.*, 2017:1). Propofol infusions might also alter the ratio of n-6 to n-3 and influence the total amount of fat given, all of which could influence ventilatory outcomes. Patients receiving immunosuppressive agents should also be excluded from studies investigating inflammatory status. Again, not all of the studies considered this as a possible confounding factor, or else they did not report clearly on this matter.

4.5 Safety and adverse events

Not all of the studies reported on the safety of n-3 FA supplementation in critically ill, MV patients or any adverse effects of such supplementation. The majority of studies that did report on this concluded that n-3 FA supplementation given either as a pure supplement or as part of an enteral or parenteral product is safe to use in this specific patient population as there were no significant differences in the occurrence of adverse events between study and control groups (Friesecke *et*

al., 2008:1416; Grau-Carmona *et al.*, 2015:34; Grau-Carmona *et al.*, 2011:582; Gupta *et al.*, 2011:112; Pontes-Arruda *et al.*, 2006:2328; Stapleton *et al.*, 2011:1660). Adverse events monitored in the trials included hepatic dysfunction, gastrointestinal complications and bleeding events (Friesecke *et al.*, 2008:1417; Grau-Carmona *et al.*, 2015:34; Grau-Carmona *et al.*, 2011:582; Gupta *et al.*, 2011:112; Pontes-Arruda *et al.*, 2006:2328; Stapleton *et al.*, 2011:1660).

It is noteworthy that Rice *et al.* (2011) observed a significantly higher frequency of diarrhoea in the group receiving the intervention, which was administered as twice daily boluses, in contrast with the other EN studies that made use of a continuous infusion method (Rice *et al.*, 2011:1577). This trial was also stopped early owing to futility (Rice *et al.*, 2011:1577). As the methodology of this particular trial differed in comparison with trials that used the same intervention, it is not possible to make definitive conclusions regarding this specific adverse event.

4.6 Limitations of this review

One of the main limitations of this systematic review relates to the lack of studies available. Although there was a relatively large sample size, not all the studies reported on the same clinical outcomes and therefore comparable data relating to each of the clinical outcomes were limited. Six of the eight enteral studies not only contained n-3 FA but also high levels of antioxidants and added GLA and, therefore, the independent effect of n-3 FA on MV cannot be determined.

The studies included also differed with regard to the primary diagnosis of the study population. Overall, the studies included patients diagnosed with ARDS, SIRS and sepsis, and also general medical and surgical ICU patients. Not only does the pathophysiology of these conditions differ, but so do the severity of inflammation and the medical management of the different conditions, thus making the different populations less comparable.

Systematic reviews are also subject to publication bias as some trials might have been missed or trials with negative results might not necessarily have been published. However, all efforts have been made to ensure that as many databases as possible were screened.

4.7 Recommendations for future research

Currently, the optimal ratio of n-6:n-3 recommended is between 2:1 and 4:1; this ratio should be implemented in future studies as the available studies differed in the ratio given and this could also influence outcomes (Donoghue *et al.*, 2017:41). No studies presently available used a third-generation lipid containing sunflower oil, MCT, olive oil and fish oil (SMOF; Fresenius Kabi) in exclusively ventilated patients and the effect of this specific lipid emulsion has yet to be determined.

There is a need for more large-scale RCTs to be performed that evaluate the different outcomes relating to MV in order for concrete recommendations to be made regarding the use of n-3 FA in this population. Ideally, these RCTs should be multi-centred trials and administer a suitable control diet that differs only with regards to n-3 FA content. Furthermore, enteral nutrition studies should be done with supplements or products that do not contain GLA and antioxidants in order to attempt to determine the separate effect of n-3 FA supplementation in ventilated critically ill patients. Alternatively, both the intervention and control diets should contain the same amount of GLA and antioxidants. The overall risk of bias across trials was high and efforts should be aimed at minimising bias in all the areas included in the assessment of risk of bias (Higgins *et al.*, 2011:6).

4.8 Conclusion

Based on the effect of n-3 FA on the inflammatory response, as well as the hasty conclusions drawn from insufficient research data currently available, products containing n-3 FA are being widely marketed and used in clinical settings based on the assumption that it has a favourable effect on not only clinical outcomes but outcomes specifically pertaining to MV. This systematic review clearly demonstrates the need for more reliable evidence in order to support this common practice and provide sufficient data that can be translated into substantiated practice recommendations.

Not only were there very few studies that met the inclusion criteria, there was great variation in the methodology of the trials which further complicates interpretation of the results. In addition to this, the trials included had an overall high risk of bias. Hence, it is not possible to draw conclusions from the currently available data as the existing trials differ radically in various key aspects including the amount of n-3 FA administered and the presence of other immunonutrients in the products used. Further research is therefore warranted and well-designed RCTs are needed in which the issues highlighted in this systematic review are adequately addressed.

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ADDENDUM A: STUDY ELIGIBILITY FORM

CRITERIA	YES	NO	COMMENTS
1. Type of study			
1.1 Randomised			
1.2 Controlled			
1.3 Blinded			
1.3.1 Double			
1.3.2 Single			
1.3.3 Open label			
2. Participants			
2.1 Age: Adults (>18 yrs)			
2.2 Mechanically ventilated			
2.3 Setting: Critically ill (admitted to ICU)			
3. Interventions			
3.1 Additional omega-3 supplement			
3.2 Omega 3-enriched product			
4. Comparisons			
4.1 Placebo			
4.2 Isocaloric, isonitrogenous, high-fat control			
4.3 Standard treatment that only differs i.t.o omission of omega 3 or with higher ratio of n6:n3			
5. Outcomes			
Primary outcomes:			
• Length of mechanical ventilation			
Secondary outcomes:			

• Route of administration of omega 3			
• Length of ICU stay			
• Mortality			

ACCEPTED	
REJECTED	

Additional notes and comments:

ADDENDUM B: CHARACTERISTICS OF INCLUDED STUDIES USING PARENTERAL NUTRITION

Friesecke *et al.* (2008)	
Methods	**Study design:** Single-centre, placebo-controlled, double-blind, randomised clinical trial **Study duration**: 7 days **Recruitment date**: January 2004 to December 2005
Participants	**Adults**: Stratified according to the presence of Systemic inflammatory response syndrome (SIRS) **Total number randomised**:166 patients; 115 patients in the group where SIRS was present; 51 patients where SIRS was absent **Country and setting**: Germany, twelve-bed medical ICU of university hospital **Inclusion criteria**: Patients were included if parenteral nutrition was indicated on grounds that enteral nutrition providing at least 25% of goal calories was impossible and was anticipated to remain impossible for longer than 6 days **Exclusion criteria**: Coagulopathy (platelets <30 000; INR >2), acute liver failure, decompensated liver cirrhosis and hypertriglyceridaemia (>4 mmol/l) **Baseline characteristics of experimental group**: 55/83 males; mean age 63 SD 13 years; 58/83 SIRS present **Baseline characteristics of control group**: 47/82 males; mean age 66 SD 11; 56/82 SIRS present
Interventions	**Standard diet**: Parenteral nutrition with a 1:1 mixture of MCT: LCT with an n-3/n-6 PUFA ratio of 1:7 (Lipofundin MCT); an amino acid solution and glucose infused separately and continuously. **Study diet**: The same MCT: LCT emulsion as the standard diet supplemented with fish oil resulting in an n-3/n-6 ratio of 1:2. The calculated dose of lipids was applied as a continuous infusion with remaining one-sixth (17%) applied as another, separate continuous infusion of the study medication (Omegaven)

	Concomitant treatment: None	
Outcomes	**Length of mechanical ventilation**: Days **Inflammatory markers**: IL-6 **ICU length of stay**: Days **Morbidity**: Nosocomial infections: Pneumonia, Urinary tract infections, Catheter-related bloodstream infections **Mortality**: 28 day mortality	
Notes	**Ethics approval**: Yes (institutional committee) **Informed consent**: Written informed consent from all patients or their next of kin **Financial contributors**: None disclosed	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation used
Allocation concealment (selection bias)	Low risk	Allocation was done by institutional pharmacy
Blinding (performance bias and detection bias)	Low risk	Double blinding Institutional pharmacy dispensed identical vials
Incomplete outcome data	High risk	IL-6 only reported in the form of a graph and not as a mean and SD as the secondary outcomes were
Selective reporting (reporting bias)	Low risk	
Other bias	None	

Barbosa *et al.* (2010)	
Methods	**Study design:** Randomised, single blinded investigation **Study duration**: Intervention given for 6 days; outcomes measured at 6 days **Recruitment date**: March – December 2007
Participants	**Adults**: 25 patients with diagnosed SIRS or sepsis and who were predicted to need parenteral nutrition were recruited at the time of admission to the ICU **Total number randomised**: Two of the 25 patients recruited did not start on parenteral nutrition and were excluded. From the 23 patients analysed, 13 received fish oil and 10 received MCT/LCT. **Country and setting**: Portugal **Inclusion criteria**: 25 patients with diagnosed SIRS or sepsis and who were predicted to need parenteral nutrition (severe pancreatitis, multi-organ failure, excisional surgery) were recruited at the time of admission to the ICU. Sepsis was defined as suspected or proven infection plus SIRS (presence of pyrexia, tachycardia, tachypnoea and/or leukocytosis). Severe sepsis was defined as sepsis with organ dysfunction (hypotension, hypoxaemia, oliguria, metabolic acidosis, and/or thrombocytopenia). Septic shock was defined as severe sepsis with hypotension despite adequate fluid resuscitation. **Exclusion criteria**: Not stated **Baseline characteristics of experimental group**: 5/13 males; age range 54 – 80 years **Baseline characteristics of control group**: 4/10 males; age range 32 – 79 years
Interventions	**Standard diet**: Patients received a 50:50 mixture of an oil rich in medium-chain fatty acids and soybean oil (termed MCT/LCT) (provided as a component of Nutriflex LipidSpecial, BBraun) **Study diet**: Patients received a 50:40:10 mixture of an oil rich in medium-chain fatty acids, soybean oil and fish oil (termed fish oil) (provided as Lipoplus, BBraun). **Concomitant treatment**: Dipeptivan (Fresenius Kabi), was included in both regimens. Both groups received electrolytes and vitamins.

Outcomes	**Plasma phospholipid fatty acid profile**: phosphatidylcholine **Inflammatory mediators in plasma**: IL-1β, IL-6, IL10, TNF-α, PGE_2, LTB_4 **Routine biochemical and physiological markers**: Full blood count, biochemistry and coagulation **Gas exchange**: pH, Lactate, PO_2, PCO_2, PF ratio, PEEP **Clinical outcomes**: 28 day mortality, Ventilated days, ICU LOS	
Notes	**Ethics approval**: The study was approved by the ethics committee from the hospital **Informed consent**: Written informed consent was obtained from each patient's closest relative **Financial contributors**: No source of support	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	Insufficient information
Allocation concealment (selection bias)	Low risk	Sealed envelope
Blinding (performance bias and detection bias)	Unclear	Insufficient information
Incomplete outcome data	Unclear	Insufficient information
Selective reporting (reporting bias)	Low risk	All outcomes were reported as per initial protocol
Other bias	None	

Gupta *et al.* (2011)	
Methods	**Study design:** Single-centre, placebo-controlled, investigator blind, prospective, randomised clinical trial **Study duration**: 14 days **Recruitment date**: 1 July 2009 – 31 December 2009
Participants	**Adults**: All patients admitted to the medical ICU of this hospital were screened for eligibility. Studied 86 consecutive patients with suspected ARDS in the first 48 hours of admission **Total number randomised**: Of the 86 patients screened, 61 were enrolled. 30 patients received the standard diet and 31 patients received the drug in addition to standard diet **Country and setting**: India **Inclusion criteria**: Bilateral pulmonary infiltrates of sudden onset in the chest radiograph, PF ratio of less than 200, and pulmonary capillary pressure less than 18 mmHg. **Exclusion criteria**: Patients were excluded for age younger than 18 or older than 80 years, pregnancy, liver failure (bilirubin >3), HIV positivity, leukopenia (<3500mm^3), thrombocytopenia (<100000 mm^3), acute bleeding, severe renal insufficiency (creatinine >2.5mg/dl) or need for renal dialysis, signs of heart failure, transplantation multiple blood transfusions, participation in other clinical trials simultaneously or in the last 60 days, treatment with nitrous oxide or corticoids (prednisolone 2mg/kg/d or equivalent), multiple organ failure, severe dyslipidemia, propofol treatment, head injury, cerebral hemorrhage, receiving immunosuppressive regimen, radiation, allergy to any of the constituents of nutritional products **Baseline characteristics of experimental group**: 19/30 males; mean age 51.16 SD 15.58 years **Baseline characteristics of control group**: 18/30 males; mean age 46.63 SD 16.44 years
Interventions	**Standard diet**: Standard isonitrogenous isocaloric enteral diet **Study diet**: Standard isonitrogenous isocaloric enteral diet supplemented with parenteral omega 3 fatty acids (Omegaven, Fresenius Kabi) **Concomitant treatment**: Not stated

Outcomes	**Oxygenation and breathing patterns**: PF ratio **Length of mechanical ventilation**: Days **ICU length of stay**: Days **Hospital length of stay**: Days **Mortality**: 28 day mortality	
Notes	**Ethics approval**: Approved by institutional ethics committee **Informed consent**: Written informed consent was obtained from all patients or their next of kin **Financial contributors**: No source of support	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated block randomisation
Allocation concealment (selection bias)	Low risk	Central allocation concealment by intensivists
Blinding (performance bias and detection bias)	Unclear	Single blinding of investigators
Incomplete outcome data	Low risk	All outcomes were reported as per initial protocol
Selective reporting (reporting bias)	Low risk	All outcomes were reported as per initial protocol
Other bias	None	

Grau-Carmona *et al.* (2015)	
Methods	**Study design:** Prospective, multicentre, randomised, comparative, double blind study **Study duration**: Intervention given for at least 5 days **Recruitment date**: Over 4 years
Participants	**Adults**: A total of 159 medical and surgical ICU patients with APACHE II score more than or equal to 13 expected to require total parenteral nutrition for at least 5 days **Total number randomised**: 175 patients underwent randomisation. Control group had 59 patients (29 drop-outs) and 58 in intervention group (29 drop-outs) **Country and setting**: Spain, 17 Spanish ICUs **Inclusion criteria**: ≥18 years old, male and female, admitted to ICU with APACHE II ≥13 were expected to require total PN for at least 5 days according to the ASPEN guidelines **Exclusion criteria**: Available online supplement **Baseline characteristics of experimental group**: 62/19 males; mean age 60.70 SD 17.29 years **Baseline characteristics of control group**: 54/78 males; mean age 60.59 SD 16.37
Interventions	**Standard diet**: Control lipid emulsion (Lipofundina, BBraun Medical) containing 50% MCT and 50% LCT **Study diet**: Lipid emulsion (Lipoplus, BBraun Medial, containing 50% MCT, 40% soybean oil (LCT) and 10% fish oil **Concomitant treatment**: Trace elements were administered according to the hospital protocol and vitamins were given from the first day of study enrollment. Enteral nutrition up to 50% of caloric requirements were allowed, did not contain any components known to exert an immune-modulatory effect
Outcomes	**Length of mechanical ventilation**: Days **ICU length of stay**: Days **Morbidity**: Prevalence of hospital-acquired infections **Mortality**: 6 months mortality **Safety of administration**: No adverse effects

	Nutritional efficacy: Actual intake of intervention and control groups	
Notes	**Ethics approval**: Protocol was approved by the clinical research ethics committees of all participating sites **Informed consent**: Voluntary informed written consents were obtained from all patients or their relatives **Financial contributors**: Sponsored by BBraun Medical S.A., Spain	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based allocation programme was used
Allocation concealment (selection bias)	Low risk	Only pharmacy service was able to deduce the type of lipid used
Blinding (performance bias and detection bias)	Low risk	Double blinding: all involved were blinded to treatment assignment
Incomplete outcome data	Low risk	All outcomes were reported as per initial protocol
Selective reporting (reporting bias)	Low risk	
Other bias	None	

ADDENDUM C: CHARACTERISTICS OF INCLUDED STUDIES USING ENTERAL NUTRITION

Pacht *et al.* (2003)	
Methods	**Study design:** Prospective, randomised, double-blind, controlled clinical trial **Study duration**: 7 days **Recruitment date**: Not reported
Participants	**Adults**: Patients between the age of 18 and 80 years who met defined criteria for ALI/ARDS **Total number randomised**: 43 **Country and setting**: Intensive care unit of the Ohio State University Medical Centre **Inclusion criteria**: Patients must have been between 18 and 80 years of age, a diagnosis of predisposing condition resulting in ALI, Bronchoalveolar lavage evidence of pulmonary inflammation as indicated by polymorphonuclear neutrophil count of >10%,one of the clinical criteria of acute lung injury/acute respiratory distress syndrome, mechanism for enteral feeding (gastric duodenal or jejunal tube feeding), chest radiography demonstrating diffuse pulmonary infiltrates, patient, legal guardian or authorised patient representative must have voluntarily signed an informed consent statement approved by the appropriate institutional review boards **Exclusion criteria**: Clinical diagnosis of left ventricular failure without bronchoalveolar lavage evidence of acute lung injury, lung cancer (primary or metastatic), haematological malignancy, acute gastrointestinal bleeding precluding enteral feeding, head trauma, stroke or subarachnoid haemorrhage, severe immunosuppression, use of steroids >0.25mg/kg/day of prednisone, use of nonsteroidal anti-inflammatory drugs within the last 24 hours, known to be HIV positive, moribund at entry, pregnancy or positive pregnancy test **Baseline characteristics**: proportion males to females not reported as a mean SD but only referred to in text as non-significant difference 60% of participants were male; mean age 62.3 SD 17.2 years There were no significant baseline differences between the two groups except for a significantly higher BMI in the intervention group reflected by a significantly higher REE.

Interventions	**Standard diet**: The control group was a ready-to-feed high- fat, low-carbohydrate enteral nutrition formula designed to reduce CO_2 production in patient with respiratory insufficiency while providing complete and balanced nutrition **Study diet**: The experimental diet (EPA + GLA) was isocaloric and isonitrogenous to the control diet, differing only in terms of its lipid composition and level of antioxidant vitamins. The lipid blend provided a mixture of EPA and DHA from fish oil and GLA from borage oil **Concomitant treatment**: None reported
Outcomes	**Assessment of Gas Exchange**: Arterial blood gases; ventilator settings **Bronchoalveolar Lavage**: IL-8, IL-6, TNF-α, LTB_4
Notes	**Ethics approval**: The study was approved by the institutional review board before patient enrolment **Informed consent**: Informed consent was obtained before any study inclusion procedures being performed **Financial contributors**: Not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were prospectively randomised to the different study groups using a permuted-block. randomisation design
Allocation concealment (selection bias)	Unclear	No detail was given with regard to the method of allocation concealment.
Blinding (performance bias and detection bias)	Low risk	All parties involved. Including clinical investigators, patients' caregivers and patients, were blinded.
Incomplete outcome data	Unclear	Insufficient information reported on whether data was reported on ITT analysis

Selective reporting (reporting bias)	Low risk	Protocol available and all outcomes reported
Other bias	None	

Pontes-Arruda *et al.* (2006)	
Methods	**Study design:** Prospective, double-blind, placebo-controlled, randomised trial (Single centre) **Study duration**: 28 days **Recruitment date**: Dates not reported. Period of recruitment was 15 months
Participants	**Adults**: Patients that were diagnosed with either severe sepsis or septic shock and who required mechanical ventilation **Total number randomised**: 165 patients randomised **Country and setting**: Patients were recruited from one medical, one cardiology and one postsurgical adult ICU in a tertiary hospital in Brazil **Inclusion criteria**: Patients >18 years of age that required mechanical ventilation having a maximum PF ration of <200 who had enteral access and a clinical diagnosis of either severe sepsis or septic shock **Exclusion criteria**: Pregnancy or breastfeeding, age<18 years, significant limitation of survival prognosis, pre-existing chronic renal insufficiency, acute pancreatitis, participation in another clinical trial <30 days before, head trauma with GCS score ≤ 5, recent stroke or subarachnoid haemorrhage, important immunological suppression, infection by HIV, no indication for enteral nutrition of imminence of receiving PN, receiving partial PN, presence of uncontrolled diarrhoea, recent gastrointestinal bleeding event, planned weaning from mechanical ventilation before study day 4, and exclusion from the protocol by physicians' decision **Baseline characteristics of experimental group**: 35/55 males; mean age 63.4 SD 18.7 years **Baseline characteristics of control group**: 26/48 males; mean age 66 SD 20 years
Interventions	**Standard diet**: High-fat, low carbohydrate enteral formula, balanced for patients with pulmonary diseases **Study diet**: enriched with supplemental EPA, GLA and antioxidants **Concomitant treatment**: Patients who remained hypotensive received steroids (hydrocortisone 200-300mg/day for 7 days in divided doses)

Outcomes	**Mortality**: 28 day mortality **Respiratory gas exchange**: PF ratio **Length of ventilation**: Ventilator-free days **ICU length of stay**: ICU-free days **Hospital length of stay**: Days **New organ dysfunction:** per system	
Notes	**Ethics approval**: Approval was obtained by the institutional review board **Informed consent**: Informed consent was obtained from patients or their legal representatives **Financial contributors**: None reported	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done in a ratio of 1:1 in a blinded way
Allocation concealment (selection bias)	Unclear	Not described by authors therefore no assessment can be done
Blinding (performance bias and detection bias)	Unclear	Not described by authors therefore no assessment can be done
Incomplete outcome data	Low risk	Intention to treat analysis was not done
Selective reporting (reporting bias)	Low risk	All outcomes reported as intended as per the methodology
Other bias	None	

Singer *et al.* (2006)	
Methods	**Study design:** Single-centre, prospective, randomised, controlled, open study **Study duration**: 14 days **Recruitment date**: February 2002 to August 2003
Participants	**Adults**: Patients with ALI/ARDS according to the American-European Consensus Conference on ARDS who were treated in the general intensive care department **Total number randomised**: 100 patients were randomised, 5 patients excluded from analysis; reasons for exclusion included introduction of steroid therapy after randomisation and severe diarrhoea. 49 patients received the control formula and 46 patients received the intervention **Country and setting**: General intensive care department of a tertiary-care, university-affiliated hospital (Tel Aviv University, Tel Aviv, Israel) **Inclusion criteria**: Patients with ALI/ARDS according to the American-European Consensus Conference on ARDS who were treated in the general intensive care department **Exclusion criteria**: Included patients with head trauma, cerebral haemorrhage, or active bleeding (because fish oil has been reported to increase coagulation disorders), patients receiving an immune-suppression regimen including >0.25mg/kg/day prednisone, HIV-positive patients, and pregnancy **Baseline characteristics of experimental group**: proportion of males to females not reported as a mean SD but only referred to in text as non-significant difference 60% of participants were male; mean age 57.0 SD 18.7 years **Baseline characteristics of control group**: proportion males to females not reported as a mean SD but only referred to in text as non-significant difference 60% of participants were male; mean age 62.3 SD 17.2 years There were no significant baseline differences between the two groups except for a significantly higher BMI in the intervention group reflected by a significantly higher REE
Interventions	**Standard diet**: The control group received a diet that was a ready-to-feed, high-fat, low-carbohydrate enteral formula (Pulmocare, Ross laboratories, Chicago, IL)

	Study diet: The study group formula (Oxepa, Ross Laboratories, Chicago, IL) diet differed from the control group diet only in lipid composition (supplemental GLA and EPA) and the level of antioxidants **Concomitant treatment**: None reported
Outcomes	**Change in oxygenation and breathing patterns**: PF ratios **Length of Mechanical Ventilation**: Assessed in hours (Ventilator hours) **Length of ICU stay**: Assessed in hours (ICU hours) **Mortality**: In-hospital mortality
Notes	**Ethics approval**: The study protocol was approved by the local institutional review board. **Informed consent**: Informed consent to participate in the study was obtained before randomisation. **Financial contributors**: Not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised to control and intervention groups by a program designed with the use of independent data management and statistical software.
Allocation concealment (selection bias)	High risk	Open-label study
Blinding (performance bias and detection bias)	Low risk	The decision to wean from mechanical ventilation was left to the discretion of physicians who were blinded to the nutritional prescription.
Incomplete outcome data	High risk	Not calculated according to ITT
Selective reporting (reporting bias)	High risk	Proportion of males to females not reported as a mean SD but only referred to in text as non-significant difference, therefore information is insufficient

Other bias	High risk	There were no significant baseline differences between the two groups except for a significantly higher BMI in the intervention group reflected by a significantly higher REE

Stapleton *et al.* (2011)	
Methods	**Study design:** Phase II randomised controlled trial **Study duration**: Patients received the study drug for 14 days **Recruitment date**: 2006-2008
Participants	**Adults**: >17 years of age (Treatment group was 49 SD 16.5 and placebo group 50.7 SD 16.5 thus still meets requirements for a systematic review with regard to age) **Total number randomised**: 90 patients randomised; control group = 49 and intervention group = 40 (one drop-out) **Country and setting**: Five North American centres **Inclusion criteria**: All intubated, mechanically ventilated patients >17 years of age meeting the ALI criteria as defined by the American-European Consensus Conference (PF ration ≤300, chest radiograph demonstrating bilateral infiltrates consistent with pulmonary oedema, and no evidence of left heart failure causing the infiltrates) were eligible for enrolment **Exclusion criteria**: Patients who met ALI criteria for ≥48 hours, expected ICU length of stay ≤48 hours, expected survival ≤ 28 days from underlying pre-ICU condition, unable to undergo BAL at enrolment, unable to obtain enteral access, pregnant, metastatic cancer, AIDS with CD4 <200, post-cardiac arrest with suspected significant anoxic brain injury, past bone marrow or solid organ transplant, platelets <30 000, active bleeding, INR >3, receiving recombinant human activated protein C, history of ventricular tachycardia or fibrillation, known allergy to fish, received enteral formula containing n-3 fatty acids during ICU stay **Baseline characteristics of experimental group**: 24/41 males; mean age 49 SD 16.5 years **Baseline characteristics of control group**: 33/49 males; mean age 50.7 SD 16.5 years
Interventions	**Standard diet**: 0.9% Saline placebo **Study diet**: Enteral fish oil (7.5cc every 6 hours equalling 9.75g EPA and 6.75 DHA daily) **Concomitant treatment**: None
Outcomes	**Inflammatory markers**: Bronchoalveolar lavage fluid (BALF) IL-8 **Length of mechanical ventilation**: Ventilator-free days

	ICU length of stay: ICU-free days **Mortality**: 60-day mortality The trial was not powered to detect differences in clinical outcomes	
Notes	**Ethics approval**: All Human Subject Committees and a Data Safety Monitoring Board (DSMB) approved the trial **Informed consent**: Informed consent obtained before randomisation **Financial contributors**: The authors received funding from NIH, ATS/ARDS Foundation and A.S.P.E.N. Nordic Naturals donated the fish oil used in this trial but had no input into the study design, study conduct, data management or publication.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random allocation in permuted blocks of four was performed
Allocation concealment (selection bias)	Low risk	Both fish oil and placebo were dispensed in opaque brown syringes by research pharmacists, and the exterior of all syringes was brushed with fish oil to preserve blinding.
Blinding (performance bias and detection bias)	Low risk	Only research pharmacists were aware of group assignment. Study participants and personnel remained blinded throughout the trial.
Incomplete outcome data	Low risk	All data collected and reported as per protocol. Reasons were provided for patient data that was not included
Selective reporting (reporting bias)	Low risk	All data collected and reported as per protocol
Other bias	None	None

Grau-Carmona *et al.* (2011)	
Methods	**Study design:** Prospective, randomised, open-label study, parallel group (Multi-centre) **Study duration**: 28 days **Recruitment date**: Not reported
Participants	**Adults**: Adult patients with the diagnosis of sepsis on admission **Total number randomised**: 160 patients were randomised **Country and setting**: 11 Spanish ICUs **Inclusion criteria**: Patients 18 years or older with a sepsis diagnosed on admission who were on mechanical ventilation and could be fed *via* the enteral route. Investigators were also allowed patients that had a probability of requiring mechanical ventilation within the first 48 hours of admission **Exclusion criteria**: Pregnant patients, patients treated with artificial nutrition in the 15 days prior to inclusion in the study or with known food allergy to an of the study die components. Patients were also excluded if they had severe hyperlipidaemia or hypertriglyceridaemia; gastrointestinal diseases precluding enteral nutrition (e.g. surgical resections, malabsorption, exacerbated inflammatory disease, persistent ileus, active upper digestive bleeding or fulminant acute pancreatitis). Other exclusion criteria included inability to position the enteral tube, immunosuppression or having received systemic immunosuppressive therapy, systemic chemotherapy in the past 3 months, autologous hematopoietic precursor cell transplantation or the existence of chronic graft-versus-host disease. Patients with advanced chronic diseases, Grade IV heart failure, functional grade IV respiratory failure, end - stage degenerative neurological processes, neoplasm, short life expectancy processes, shock of any aetiology with multiple organ failure or post-cardiopulmonary resuscitation with serious neurological damage 72 hours after arrest were also excluded **Baseline characteristics of experimental group**: 62/80 males; mean age 62 IQR 40-71 years **Baseline characteristics of control group**: 68/80 males; mean age 65 IQR 51-75.9 years Baseline characteristics were not significantly different between the two

Interventions	**Standard diet**: Ensure Plus HN (Abbott Laboratories, Madrid, Spain) **Study diet**: Oxepa (Abbott Laboratories, Madrid, Spain) **Concomitant treatment**: None stated	
Outcomes	**Finding new organ dysfunction**: SOFA **Oxygenation**: PF ratio **Length of ventilation**: Days **ICU length of stay**: Days **Hospital length of stay**: Days **Morbidity**: Incidence of nosocomial infection **Mortality**: 28 day mortality	
Notes	**Ethics approval**: The protocol for the study was approved by the local Institutional Review Board of every hospital participating. Approval was obtained before patient recruitment began **Informed consent**: Obtained from patients or their legal representatives. This was done before randomisation **Financial contributors**: Authors reported that sources of funding had no role in acquisition, analysis or the interpretation of data. Funding sources also had no role in the submission of the report.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done by a computer-generated random-numbers table. Competitive recruitment between participating centres was allowed until any centre reached a maximum of 20% of the calculated size
Allocation concealment (selection bias)	Low risk	None
Blinding (performance bias and detection bias)	Low risk	Patients were blinded to diet administration

Incomplete outcome data	High risk	ITT analysis not done
Selective reporting (reporting bias)	Low risk	All outcomes reported as intended as per the methodology
Other bias	None	

Rice *et al.* (2011)	
Methods	**Study design:** Randomised, double-blind, placebo-controlled, multicentre trial **Study duration**: Dosing of the intervention continued until the earliest of 21 days, 48 hours of unassisted breathing, or extubation. **Recruitment date**: 2 January 2008 to 21 February 2009
Participants	**Adults**: Participants were 272 adults within 48 hours of developing acute lung injury requiring mechanical ventilation whose physicians intended to start enteral nutrition **Total number randomised**: 272 patients randomised, 143 in the experimental group and 129 in the control group **Country and setting**: USA, multicentre trial **Inclusion criteria**: Patients with ALI requiring mechanical ventilation whose physicians intended to start enteral nutrition were eligible for inclusion. Specifically, patients had to be receiving mechanical ventilation, have a ration of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) of less than 300 (adjusted if the altitude exceeded 1000m), and have bilateral pulmonary infiltrates consistent with oedema on chest radiograph without clinical evidence of left arterial hypertension **Exclusion criteria**: Severe chronic lung disease, time window (acute lung injury >48 hours or intubated >72 hours, inability to obtain consent, likely fatal underlying disease, recent intracranial haemorrhage, severe liver disease, refractory shock, coagulopathy, refused consent **Baseline characteristics of experimental group**: 78/143 males; mean age 55.5 SD 17 years **Baseline characteristics of control group**: 64/129 males; mean age 52.9 SD 16.5 years
Interventions	**Standard diet**: The control supplement (Isocaloric-isovolumic) was administered enterally as twice-daily boluses of 120ml beginning within 6 hours of randomisation and was identical in appearance and smell to the deodorised n-3 supplement. **Study diet**: The n-3 supplement was administered enterally as twice-daily boluses of 120ml beginning within 6 hours of randomisation.

	Concomitant treatment: Institution-specific insulin protocols were used to target blood glucose ranges of 80 to 150 mg/dL. Patients were also simultaneously randomised to a separate ongoing trial (the EDEN study) comparing low- vs full-calorie enteral nutrition in a 2x2 factorial design.	
Outcomes	**Ventilator-free days**: This was defined as the number of days alive and breathing without assistance from randomisation to day 28. **Morbidity**: Number of organ failure-free days, development of new infections, frequency of gastrointestinal intolerance. **Mortality**: 60-day mortality before hospital discharge with unassisted breathing.	
Notes	**Ethics approval**: The trial was approved by the institutional review board at each of the 44 enrolling hospitals **Informed consent**: Written informed consent was obtained from every patient or surrogate prior to any study procedure **Financial contributors**: This study was supported by the National Heart, Lung and Blood Institute (NHLBI). Abbott Nutrition, Columbus, Ohio provided the Omega-3 fatty acid, γ-linolenic acid, and antioxidant and control supplements in the study. Neither the NHLBI nor Abbott Nutrition had any role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised web-based software used for randomisation
Allocation concealment (selection bias)	Low risk	It was stated that the control was identical in appearance and smell to the deodorised n-3 supplement
Blinding (performance bias and detection bias)	Low risk	Study was double blind
Incomplete outcome data	Low risk	Study was stopped for futility at the first interim analysis after randomisation of

		143 patients to the n-3 group and 129 patients to the control group
Selective reporting (reporting bias)	Low risk	Protocol available and all outcomes reported
Other bias	High risk	Baseline imbalances: The n-3 group had higher minute ventilation. The study was stopped early due to futility

Parish *et al.* (2014)	
Methods	**Study design:** Randomised clinical trial **Study duration**: 14 days **Recruitment date**: June 2011 to September 2013
Participants	**Adults**: All patients were under mechanical ventilation with volume-controlled mode with low tidal volume strategy and fluid conservative haemodynamic management protocols. **Total number randomised**: 58 patients randomised, 29 patients in each group **Country and setting**: Iran, 2 ICUs of Tabriz University **Inclusion criteria**: 58 patients with 100<PF ratio<300, bilateral infiltration, acute onset (<6days) and ability to tolerate enteral nutrition were enrolled in this study **Exclusion criteria**: Age < 18 years old, plasma triglycerides more than 400mg/dl, liver and kidney failure, platelets less than 50000µl, leukocyte count less than 3 x 10^9/L and previous history of frequent transfusion **Baseline characteristics of experimental group**: 16/27 males; mean age 64.4 SD 10.2 years **Baseline characteristics of control group**: 15/27 males; mean age 62.7 SD 13.7 years Baseline characteristics were not significantly different between the two groups
Interventions	**Standard diet**: 25kcal/kg enteral formula/day (isocaloric, isovolemic, carbohydrate-rich, 1kcal/cc) *via* nasogastric tube or PEG feeding tube **Study diet**: In intervention group, patients received 6 omega 3 soft gels per day (2 capsules every 8 hours) in addition to standard treatment. Every 2 soft gels deliver 720mg of Omega 3 including 600mg of EPA and DHA (360mg EPA/240mg DHA) **Concomitant treatment**: None stated
Outcomes	**Oxygenation parameters**: PaO_2, $PaCO_2$, SaO_2, pH, Compliance, Resistance, PF ratio, P plateau, V_T **ICU length of stay**: Days

	Morbidity: Number of organ failures **Mortality**: 28-day mortality	
Notes	**Ethics approval**: Ethics committee approval from Tabriz University of Medical Sciences **Informed consent**: Informed consent was given from next of kin **Financial contributors**: None disclosed, reported no conflict of interest	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised web-based software used for randomisation
Allocation concealment (selection bias)	High risk	No allocation concealment done
Blinding (performance bias and detection bias)	High risk	No method of blinding reported
Incomplete outcome data	Low risk	All patients randomised were included in the analysis and there were no drop-outs or major adverse events reported.
Selective reporting (reporting bias)	Low risk	Protocol available and all outcomes reported
Other bias	None	

Kagan *et al.* (2015)	
Methods	**Study design:** Single-centre, prospective, randomised, comparative, double-blind study **Study duration**: 7 days **Recruitment date**: November 2010 to June 2014
Participants	**Adults**: Patients with severe trauma requiring mechanical ventilation **Total number randomised**: 120 patients randomised **Country and setting**: General ICU of the Rabin Medical Centre, Petah Tikva, Israel, a tertiary care level 1 trauma centre of a university-affiliated hospital **Inclusion criteria**: All patients between the ages of 18 and 90 years with a diagnosis of multiple trauma, defined as physical insults or injuries occurring simultaneously in more than one part of the body, or of isolated head trauma that required mechanical ventilation and had an anticipated ICU stay of ≥2 days were included in the study. **Exclusion criteria**: the presence of any contraindication for commencing EN within the first 36h of ICU admission, such as mechanical or functional small bowel obstruction, high-output fistula, gastrointestinal tract discontinuity and/or surgeon reluctance to commence EN immediately following abdominal surgery; treatment with immunosuppressive drugs; second-/third-degree burns covering >66% of body surface area; pregnancy **Baseline characteristics of experimental group**: 49/62 males; mean age 42.9 SD 18.6 years **Baseline characteristics of control group**: 47/58 males; mean age 38.4 SD 16.8 years Baseline characteristics were not significantly different between the two groups except for the number of patients suffering from isolated head trauma.
Interventions	**Standard diet**: The control group who received a high-fat, low-carbohydrates enteral formula (Pulmocare; Ross laboratories, Chicago, IL) **Study diet**: a study group who received a formula enriched with supplemental EPA, GLA and antioxidants (Oxepa: Ross laboratories)

	Concomitant treatment: None stated	
Outcomes	**Level of Oxygenation**: PF ratio **Duration of ventilation**: Days **ICU length of stay**: Days **Hospital length of stay**: Days **Morbidity**: Incidence of new failure as measured by the daily SOFA score, rate of infections including wound infections **Mortality**: 28 day mortality	
Notes	**Ethics approval**: The study protocol was approved by the local institutional review board. **Informed consent**: Informed consent was obtained prior to randomisation either from the patient or his/her legal representative if possible, or from an independent physician where this was not possible. **Financial contributors**: None disclosed, reported no conflict of interest	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based block randomisation generated by a statistical software program which was concealed from all investigators apart from the principal investigator
Allocation concealment (selection bias)	Low risk	The two feeds were decanted from their commercial packaging and presented at the bedside in a blinded manner.
Blinding (performance bias and detection bias)	Low risk	All healthcare workers involved in the daily care of the patients were blinded to the type of EN administered.

Incomplete outcome data	Low risk	Intention to treat analysis done, no major adverse events reported. Reasons provided for drop-outs
Selective reporting (reporting bias)	Low risk	All outcomes reported as intended as per the methodology
Other bias	None	

ADDENDUM D: PRISMA CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	34
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	36
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	37
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	38
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	39
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	38
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	39
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	39

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	39-40
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	39
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	39
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^{2}) for each meta-analysis.	39-40